



VOLUME XXV

1946

# MEDICINE

*Analytical Reviews*  
of  
General Medicine  
Neurology and Pediatrics

EDITORIAL BOARD

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ALAN M. CHESNEY

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# MURINE TYPHUS FEVER<sup>1</sup>

EDWARD S MILLER AND PAUL B BEESON

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## INTRODUCTION

For more than 30 years it has been known that a form of typhus fever is endemic in the southern part of the United States. Conditions appear to exist whereby the disease may become a problem elsewhere in the country, since the

<sup>1</sup> Received for publication September 8, 1944

rat and rat flea—natural host and vector—are widely distributed. The recent recognition of cases in Maryland, West Virginia, Ohio, Arkansas, Iowa and California suggests that wider dissemination of murine typhus may actually be taking place (21)

The clinical picture of this disease is distinctive, and a diagnosis can be made with considerable certainty by those who are familiar with it. Many physicians, however, have not had an opportunity to observe cases at first hand. Most of the existing descriptions have been written by field workers who did not have the advantage of detailed case study which hospital practice affords, the only report of a series of cases treated in a single hospital is that of Joseph, which is based on 44 cases at Charity Hospital, New Orleans, La (13). The present article deals with an analysis of 126 cases seen at Grady Hospital, Atlanta, Ga. Special attention is devoted to the clinical and laboratory diagnosis. In addition, because of past confusion in respect to the nomenclature of this and other rickettsial infections, there is included a brief introductory survey of present concepts of the etiology and terminology of the American rickettsial diseases.

#### RICKETTSIAL DISEASES IN THE UNITED STATES

*Classical Typhus* (Synonyms epidemic typhus, European louse-borne typhus, Old World typhus) This is the form of typhus which has occurred in great epidemics in Europe and elsewhere for hundreds of years. Epidemics occurred in America in the 16th, 17th, 18th and 19th centuries. Gerhard of Philadelphia, in the early part of the 19th century, was the first to differentiate between typhoid and typhus fevers.

The etiological agent of classical typhus is the *Rickettsia prowazeki*. Infection is transmitted from man to man by the body louse. The reservoir of infection, at least during epidemics, is man. The identity of the natural host during inter-epidemic periods has not been established, although man may also serve in that capacity, since there are individuals who suffer recurrences years after their initial attacks (27). Cases of this type constitute the only instances of classical typhus now seen in America.

*Murine Typhus* (Synonym Endemic typhus) Typhus was first recognized in the South in 1913, when Paullin reported 6 cases from Atlanta, Ga (17). Shortly afterward the disease was found in North Carolina and in Texas. Because the clinical picture was similar to that which had been described by Brill in New York (see below), the name "Brill's Disease" began to be applied to the cases seen in the southern states. However, Maxcy, in 1926, emphasized differences between typhus fever in the South, and that which occurred along the northeastern seaboard and in Europe (15). He found no evidence of louse transmission in the southern cases, and suggested that the rat may serve as the reservoir of infection. This was later established as a fact by Dyer and his associates, who also demonstrated that the rat flea can act as a vector (9, 10). It was further noted that inoculation of guinea pigs with typhus strains isolated in the southern United States led to intense scrotal inflammation, (16) a lesion which did not occur during infection with strains from the European form of

typhus With all of this evidence it became obvious that the typhus in the southern United States is a different disease from the classical variety The etiological agent of murine typhus, which has been named the *Rickettsia mooseri*, is similar to, but not identical with, the *Rickettsia prowazeki* The disease can be transmitted from rat to rat by the rat flea and the rat louse, and from rat to man by the rat flea Murine typhus infection has also been discovered in house mice, the significance of this reservoir in relation to human disease remains to be decided (6) Under certain conditions the infection can also be transmitted from man to man by the body louse In this way epidemics of the disease can occur, as has been the case in Mexico (29) Whether insect vectors provide the only means of infection with murine typhus is open to question Rickettsiae are present in the urine of infected rats, and it has been shown that murine typhus can be transmitted to rats by the feeding of infectious material (25) It is conceivable that human beings also may become infected by the inhalation or the ingestion of material contaminated with rat urine Many laboratory workers who have handled high concentrations of the rickettsiae have developed typhus, in these cases the portal of entry is presumed to be the respiratory tract Later in this article it will be noted that a history of flea bite was rarely given by our patients

**Brill's Disease** Between 1898 and 1911, Brill (7) described a series of cases in New York which bore a striking resemblance to European typhus Brill, however, was unwilling to designate them as such because the circumstances of infection were so different from those which are usually present in European typhus When animal experiments revealed that there was a cross immunity between Brill's Disease and American strains of typhus (from Mexico) (1), it was generally assumed that they were the same disease This belief was challenged later by Zinsser and Castaneda, who showed that the rickettsiae isolated from cases of Brill's Disease had the characteristics of the classical type, rather than the murine variety (30) Zinsser then carried out a fruitful epidemiological study of the disease as seen along the northeastern seaboard (27) He found that 94.8 per cent of the cases had occurred in foreign born individuals, chiefly Jews, who had immigrated to this country from typhus regions of central Europe He therefore postulated that Brill's Disease represented a recurrence of latent infection of classical typhus fever Recently his conclusions have been corroborated by Plotz (19) who used the complement fixation test with rickettsial suspensions as antigens to demonstrate the immunologic identity of Brill's Disease with classical typhus These facts are sufficient, in our opinion, to establish Brill's Disease as a sporadic form of classical typhus It is apparently the only variety of classical typhus now present in the United States Nearly all reported cases have occurred in the large cities of the northeastern section of the country, since the majority of immigrants from central Europe settled there The possibility exists that such recrudescences could give rise to epidemics of classical typhus fever in the United States even now, in places where overcrowding and louse-infestation are present

At this point a comment on the nomenclature of the varieties of typhus fevers

seems appropriate. In the course of years scores of names have appeared and time has proved many of them to be ill-chosen. Zinsser has emphasized the point that both of the two major types of typhus may be either endemic or epidemic and that both may be louse-borne. Likewise, neither is limited to any one geographical region. We have used the term "classical typhus" to indicate that variety which is caused by the *Rickettsia prowazekii*, is usually louse-borne and is prevalent in Europe. The kind which is endemic in the southern United States, whose etiological agent is the *Rickettsia mooseri*, and whose natural reservoir is the rat, is most aptly termed "murine typhus." "Brill's Disease" is frequently used as a synonym for the latter, but since the cases which Brill described actually appear to have been recrudescences of previously-acquired classical typhus, there is no justification for the application of that name to murine typhus.

**Rocky Mountain Spotted Fever** Of the other rickettsial diseases which occur in the United States, Rocky Mountain Spotted Fever is the one which could be confused clinically with murine typhus. The causative organism has been named the *Rickettsia rickettsii*. Several species of ticks are the natural vectors. At least one of these (*Dermacentor andersoni*) serves likewise as a reservoir of infection, since the disease is hereditary in that arthropod. Other reservoirs are in rodents and dogs. Rocky Mountain Spotted Fever has been reported in nearly all sections of the country, including those in which murine typhus is endemic. This disease is usually of greater clinical severity than murine typhus, and also differs in the distribution of the rash. For laboratory differentiation from typhus the complement fixation test is apparently reliable (4). The Weil-Felix reaction is positive in Rocky Mountain Spotted Fever just as it is in the typhus fevers.

**American Q Fever** Another tick-borne rickettsial infection has been found in this country, chiefly in the Northwestern states (8). It was first described in Queensland, Australia, and thus came to be known as Q fever. The causative organism has been called either *Rickettsia diaporica* or *Rickettsia burneti*. The disease is not accompanied by a rash, may take the form of an atypical pneumonia, and bears little resemblance to murine typhus (12). The Weil-Felix reaction is negative.

**Bullis Fever** A new rickettsial disease has recently been discovered at Camp Bullis in Texas and has been called "Bullis fever." It is tick-borne, and is characterized by fever and a rash. The Weil-Felix reaction is negative (2, 14, 26).

#### LABORATORY PROCEDURE USED IN THE DIAGNOSIS OF MURINE TYPHUS

**Isolation of the Causative Agent** The organism can be isolated in the early stage of the disease by inoculating a guinea pig with the patient's blood. This method of diagnosis is, however, not practical, since it is time-consuming, requires an expert observer and carries with it a not inconsiderable risk of infection among the laboratory personnel.

**Weil-Felix Reaction** This test, which depends on the agglutination of the

0X19 strain of the proteus bacillus is the most useful routine laboratory procedure for the diagnosis of murine typhus. Zinsser has discussed the coincidence by which it was discovered, and the probable immuno-chemical basis (28). The reaction usually becomes positive during the second or third week of illness. A serum titer of 1 to 160 or higher is generally diagnostic of typhus, particularly if there is a rising titer during the course of the illness. The Weil-Felix reaction is positive in classical typhus and in Rocky Mountain Spotted Fever, as well as in murine typhus. Furthermore, it may be positive in persons who have recently suffered from *Proteus* bacillus infection.

*The Complement Fixation Test Using Rickettsial Suspensions as Antigens* This is apparently more specific in differentiating the various rickettsial diseases than is the Weil-Felix reaction, but unfortunately is not yet available in routine clinical laboratories (4, 19).

*Biopsy* In patients who have a rash, an early diagnosis can be made by an experienced pathologist, from a biopsy of one of the skin lesions (18). Tissue for this can be obtained readily at the bedside by the use of a skin-punch biopsy instrument. The specimen should be fixed in Regand's solution and stained by the Giemsa method. The characteristic changes consist of an inflammatory process involving the small blood vessels, with proliferation of the endothelium. Thrombus formation, such as is seen in classical typhus, is relatively uncommon. Rickettsial bodies can be identified in the endothelium by experienced observers. However, even without this the pattern of the lesion itself is usually sufficiently characteristic to point strongly toward a diagnosis of typhus.

#### CLINICAL MATERIAL USED IN THE PRESENT ANALYSIS

The records of 126 patients who were treated in Grady Hospital during the 8-year period from 1936 through 1943 were selected for analysis. Only cases in which the diagnosis of typhus had been established beyond reasonable doubt were included. The principal criteria for this selection were a clinical course consistent with the diagnosis, and a positive Weil-Felix reaction in a titer of 1 to 160 or higher. Among the rejected cases were several which were consistent from the standpoint of clinical course, but in which the serologic test remained negative. These, of course, may have been typhus fever, since a positive serologic reaction is seldom found in 100 per cent of cases of any infection. In several other instances the Weil-Felix reaction had been positive, but its significance could not be assessed because of *Proteus* bacillus infection of the urinary tract. It is particularly important to note that among the rejected cases were 3 fatalities. In these cases death occurred before a positive Weil-Felix reaction could have been expected. They will be mentioned again in the section on "Outcome."

#### EPIDEMIOLOGICAL DATA ON 126 CASES OF MURINE TYPHUS

*Age* Table I shows the distribution of the patients in this series, according to age, sex and race. While the disease appeared in all the decades of life, nearly half of the patients were between 20 and 40 years of age. This is usual in murine



typhus, and is probably attributable to occupational exposure to infection. It will be noted that only 3 patients were under the age of 10, this figure is not a true index, since our material did not include the records of colored patients under 12 years of age.

*Sex* Of the 126 patients, 82 were males and 44 were females, a ratio of almost 2 to 1. This is in accord with other experience (20), and is usually thought to be due to greater occupational exposure in men.

*Race* Murine typhus is usually thought to be much more common in white people than in negroes. Maxcy and others concluded on the basis of reported cases from several southern states that the attack rate in the white population is 7 to 10 times as high as that in the colored race (3, 5, 15). It is therefore of considerable interest to note that more than half of the patients in our series were negroes. When the rates were computed in relation to total admissions to the hospital during the same 8-year period it was found that there were 7.5 cases of

TABLE I

*Distribution of 126 Cases of Murine Typhus, According to Age, Sex, and Race*

AGE GROUP	WHITE		NEGRO	
	Male	Female	Male	Female
0-9		3		
10-19	7	4	7	3
20-29	9	3	14	9
30-39	5	5	17	2
40-49	4	5	4	3
50-59	5	3	5	2
60-69	4	1	1	1
+70				
Total	34	24	48	20

murine typhus for each 10,000 white admissions, and 7.9 cases for each 10,000 negro admissions. Admitting that the experience of a single hospital may not be applicable to the population as a whole, nevertheless it appears to us that the racial immunity of the negro has been exaggerated. Tucker and co-workers came to the same conclusion after studying several localized outbreaks of murine typhus in Nashville, Tenn. (22). Possible explanations for the low number of reported cases among negroes are the facts that the rash often cannot be seen in negroes and that medical care and case-reporting are inadequate in that race.

*Yearly and Seasonal Variation* Table II gives the distribution of the 126 cases in this series, according to the month of admission, during the 8-year period. It will be noted that there was an increase in the frequency with which murine typhus was diagnosed in this hospital during the period of this study. It is impossible to say whether this represents a true increase in the incidence of the disease in Atlanta, or whether the figures simply reflect an improvement in the clinical recognition of the disease.

There is a marked seasonal variation in the prevalence of typhus in Atlanta, as also shown in Table II. Nearly 78 per cent of the cases occurred during the months of August, September, October and November. This preponderance of cases in the late summer and autumn had been found in other studies on typhus (5), but the reason for its occurrence has not been satisfactorily explained. Possibly it is related to the fact that flea infestation of rats is greater in warm weather (11).

*Occupation* Maxey noted that employees of food-handling establishments were particularly vulnerable to typhus infection (15). This appears to be explainable on the basis of the frequency with which such establishments are infested with rats. A study of the occupations of the 126 persons in this group revealed that 34, or 27 per cent of them, were employed as food handlers, in restaurants, market places, produce and feed stores.

TABLE II

*Month and Year of Admission to the Hospital, in 126 Cases of Murine Typhus*

YEAR	JAN	FEB	MAR.	APR.	MAY	JUNE	JULY	AUG.	SEPT	OCT	NOV	DEC.	TOTAL
1936							1		1				2
1937							2	2	1		1		6
1938						1		1	1	5	2	1	11
1939	1				2		1	5	6	3	3	1	22
1940								1	3	2	4		10
1941	2					1		1	5	6		4	19
1942						1		4	7	9	3		24
1943		2					7	5	8	5	4	1	32
Total	3	2			2	3	11	19	32	30	17	7	126

*Contact with Rats and Fleas* Sixty-eight, or 54 per cent, of the records stated that there had been contact with rats, and in only 6 per cent of the cases was such contact specifically denied. Only 2 of the patients, however, could recall having been bitten by fleas. As was mentioned previously, this is one of the points which has made us question the necessity of actual contact with fleas in order that infection of human beings can occur. The feces of fleas and the urine of infected rats may contain rickettsiae, and it may be that the inhalation or ingestion of dust contaminated with this material can be a mode of infection.

*Contact between Cases* Murine typhus usually occurs sporadically, any relationship between cases is probably due to common opportunities for exposure, rather than contagiousness of the human disease. We have observed case groupings of this type. During one period of several weeks there were 6 cases among negro male employees of a large feed mill. This establishment was notorious for rat infestation, and had been the source of other cases of typhus in previous years. On another occasion there were 4 typhus patients in the hospital at the same time, all of whom lived on the same city block (but no 2 from one house). Their homes were adjacent to a cotton mill, and the neighborhood

was over-run with rats. Finally, there was one small family outbreak, involving a mother and her 2 young children, these people lived near a farmers' market place.

### CLINICAL FEATURES OF 126 CASES OF MURINE TYPHUS

The clinical features of murine typhus are fairly constant and distinctive. The onset of illness is usually abrupt, often with a chill. There is a sustained fever. Headache is nearly always present. A rash appears about the 5th day. The illness is self-limited, usually terminating during the third week. Complications are few and the fatality rate is low.

*Onset*—An abrupt onset was an outstanding feature of the clinical picture in this series of cases. In approximately one-half of the patients the illness was well established within 24 hours after the appearance of the first symptom. In an additional 40 per cent the abrupt onset of severe illness was preceded for a

TABLE III  
*Principal Symptoms in 126 Cases of Murine Typhus*

SYMPTOM	PRESENT		ABSENT		NOT MENTIONED	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
Headache	114	91	4	3	8	6
Muscular Aching	111	88	5	4	10	8
Chills	90	71	27	21	9	7
Anorexia	80	63	12	10	34	27
Cough	68	54	34	27	24	19
Vomiting	61	48	57	45	8	6
Photophobia	29	23	19	15	78	62
Constipation	26	21	43	34	57	45
Sore Throat	16	13	—	—	110	87
Diarrhea	13	10	43	34	70	56

few days by mild premonitory symptoms, principally aching, headache, feverishness, coryza, anorexia and cough. Finally, in a few cases the onset was intermediate in type, without a prodromal period, but with the development of the full-blown illness occurring over a period of 2 or 3 days.

*Symptoms*—The chief symptoms of the 126 patients are listed in Table III. They are symptoms which occur with many acute infectious diseases, and no one of them is sufficiently distinctive to the pathognomonic of murine typhus. Headache was the most frequent complaint, and many patients considered it the worst feature of the illness. It was usually frontal, but occasionally occipital in distribution. It appeared early and often lasted throughout the febrile period, varying in intensity with the rise and fall of the fever and gradually diminishing during defervescence. Efforts to relieve the headache by means of common analgesics resulted in only partial relief. Muscular aching and malaise were nearly as common as headache. They were frequently associated with moderate muscular tenderness. The aching involved particularly the lumbar

region, the legs, the shoulder and upper arm muscles and the back of the neck. Occasionally there was pain in the abdomen, suggesting the possibility of a surgical condition, in fact, one of these patients was subjected to an appendectomy because of lower abdominal pain and tenderness. Chills occurred in 90 of the 126 cases, usually during the first week of illness. Not infrequently a chill was the initial symptom. In 61 of the 90 cases, there were repeated chills, some patients experienced as many as 15 or 20. *Gastrointestinal complaints* were numerous. All except a few patients had anorexia, and in half of the cases there were one or more episodes of vomiting. Twenty per cent of the patients were troubled by constipation and 10 per cent had diarrhea, however, the symptom of diarrhea is common in this class of patients, because many of them take

TABLE IV  
*Percentage of White and Negro Patients Who Had a Skin Rash*

RACE	NUMBER OF CASES	NUMBER WITH RASH	PER CENT WITH RASH
White	58	52	90
Negro	68	29	43
Total	126	81	64

TABLE V  
*Location of the Skin Rash in 81 Cases of Murine Typhus*

LOCATION	NUMBER	PER CENT
Trunk	79	98
Upper extremities	61	75
Lower extremities	48	59
Palms	11	14
Soles	8	10
Face	8	10

laxatives at the first sign of illness. Cough occurred in 54 per cent of the cases. It was usually non productive or accompanied by only small quantities of mucoid sputum. In 6 cases the sputum was described as blood tinged or rusty. *Photophobia* of moderate degree was noted in 23 per cent of the cases, and *sore throat* in 13 per cent.

*Physical Findings.* On admission the patients generally appeared acutely ill and were uncomfortable because of muscular pains or headache. As to the severity of the illness, 100 of the 126 cases were described as moderately ill. Frank delirium was present in 21 of the 126 cases and some diminution in the level of awareness was noted in an additional 28 patients. The remaining 77 were mentally clear.

The skin eruption is the most helpful physical finding leading to the diagnosis of typhus. It does not occur invariably, however, only 81 of the 126 cases in this series had a rash. As is shown in Table IV, a rash was found in less than

half of the negro patients, while it was present in 90 per cent of the white patients. This discrepancy undoubtedly results from the difficulty in identifying a rash on deeply pigmented skin. It may account in part for the small number of cases reported in negroes. The rash of typhus is rather distinctive. The lesions are 3 to 10 mm in diameter, macular or papular, and not confluent. At first they are pink to dull red in color and blanch on pressure. Occasionally they are hemorrhagic. As the rash matures it no longer disappears with pressure, but assumes a brownish hue, and then fades. In Table V is shown the location of the rash in this group of cases. It was present on the trunk almost without exception, being most profuse on the chest and abdomen, and less extensive on the back. Lesions were also frequent on the proximal segments of the extremities. There was only occasional involvement of the palms, soles and face in the form of erythematous macules. It is usually said that the rash appears between the 4th and 8th days of illness. We were unable to obtain reliable information on this point, beyond the fact that rash was present at the time of admission to the hospital in 74 of the 81 cases. The lesions usually have disappeared completely by the time the fever is gone. Conjunctival injection was noted in 86 cases (68 per cent). It was usually moderate in degree, but occasionally there were small sub-conjunctival hemorrhages.

Nearly all of the patients appeared dehydrated at the time of admission. There was diffuse reddening of the throat in 52 cases (41 per cent). Lymph node enlargement was not noteworthy. Physical examination of the chest was essentially negative except for a few patients who had bronchial wheezes, rhonchi, or scattered basal rales. X-rays of the chest were obtained in 71 cases. A number of them showed accentuation of hilar markings, but there were no other abnormalities attributable to typhus fever. The spleen was palpable in 35 cases (28 per cent). It was usually moderately firm, and diminished in size during the convalescent period. There was no significant liver enlargement. Neurologic signs were rare, aside from occasional delirium, already mentioned. In 8 cases (6 per cent) there was slight stiffness of the neck. Moderate muscular tenderness was quite common.

*Course of Illness* The majority of the patients in this series were admitted to the hospital between the 4th and 8th day of illness. The symptoms usually remained at about the same intensity for the first 8 to 10 days of disease, then gradually diminished during the following week. We encountered no instance of relapse of typhus fever.

The temperature curve is a characteristic feature of the disease. In calculating the duration of fever in this series of cases the initial appearance of the fever was considered to coincide with the abrupt onset of illness whether or not there had been prodromal symptoms. Table VI gives the duration of fever on this basis, in all cases except those in which some complicating infection had obviously prolonged the fever. In approximately half the cases the duration of fever was between 13 and 17 days, the extremes of variation being from 9 to 25 days. During the first 8 to 12 days the temperature usually ranged between 103° and 105° F, after this the level began to slope downward. In most in-

stances defervescence took place over a period of 2 to 7 days, and during defervescence the daily variations were more marked than in the early stages of the disease.

TABLE VI  
*Duration of Fever in 126 Cases of Murine Typhus*

DURATION OF FEVER	NUMBER OF CASES
<i>days</i>	
9	1
10	2
11	8
12	6
13	11
14	14
15	7
16	15
17	12
18	4
19	5
20	5
21	7
22	10
23	3
24	1
25	2
Not Estimated	18

#### LABORATORY DATA ON 126 CASES OF MURINE TYPHUS

**Weil-Felix Reaction.** A positive Weil-Felix test was one of the criteria for the selection of the cases for this series, consequently all of the patients had a serum agglutination titer of at least 1 to 160 at some time during the period of observation. The rate of appearance of antibodies was found to be variable. In some instances a significant titer was found as early as the 5th day of illness, while in other cases it did not develop until the 20th day. In most patients a rising titer was demonstrated and the highest levels occurred during the period of early convalescence. Data were not available on the duration of the reaction after recovery. Table VII lists the titers found on admission, as well as the highest attained, in the last 55 cases in this series. The data on the earlier cases were not tabulated, because in many instances the test had not been carried to maximum serum dilutions.

**Anamnestic Agglutination Reactions.** In 27 of the 126 cases there was, at the time of the development of the positive Weil-Felix reaction, agglutination of one or more other antigens—Typhoid "H", Typhoid "O", Paratyphoid B or Brucella—in a titer of 1 to 80 or higher, occasionally reaching such levels as 1 to 640 or 1 to 1280. These reactions were usually transient and the agglutination titer for the *Proteus* OX19 was always higher. These points, together with

the fact that the clinical features were characteristic of typhus, made it seem reasonable to regard the other agglutinations as anamnestic phenomena

*Leucocyte Counts* Leucocyte counts were usually determined several times in each of these cases Table VIII shows the levels of the leucocyte counts at the time of admission, as well as the highest and lowest figures for each patient In tabulating this material we eliminated all cases in which there was some complication which might have affected the leucocyte count The lowest count

TABLE VII

*Admission and Maximum Weil-Felix Titers in 55 Cases of Murine Typhus*

TITER	ON ADMISSION TO HOSPITAL	HIGHEST TITER REACHED
0	11	
40	10	
80	9	
160	6	2
320	10	11
640	4	6
1280	3	12
2560	1	10
5120	1	8
10240		5
20480		1

TABLE VIII

*Admission, Highest and Lowest Leucocyte Counts in 108 Cases of Murine Typhus*

LEUCOCYTE COUNT	ON ADMISSION	HIGHEST	LOWEST
0-1900	1	0	1
2000-3900	3	0	5
4000-5900	21	3	22
6000-7900	29	27	36
8000-9900	21	36	19
10000-11900	20	14	17
12000-13900	5	8	2
14000-15900	1	5	
16000-17900	2	6	1
18000-19900		2	
20000-21900		2	

recorded was 1,500 and the highest 20,800 In the majority of cases, however, the white blood cell count fell within normal limits The differential counts usually revealed a normal distribution, occasionally there was a moderate increase in polymorphonuclear cells

*Urinalyses* Urinalyses frequently showed the presence of a small amount of albumin and a few granular casts during the early period of illness, but other than this there were no urinary abnormalities

*Sedimentation Rates* Sedimentation rates, determined by the Westergren

method, ranged from 2 mm to 120 mm per hour, but in the majority of cases the rates were from 30 mm to 80 mm during the febrile stage

*Spinal Fluids* The cerebrospinal fluid was examined in 45 cases. In one group of 8 cases the fluids were abnormal, but these 8 patients all had positive blood serologic tests for syphilis, hence it was impossible to interpret the findings with reference to typhus. On the other hand, there were 9 cases in which blood serologic tests for syphilis were positive, but in which the spinal fluid findings were entirely normal. In the remaining 28 cases there was no past or present evidence of syphilis. In these the spinal fluid pressure, total protein, Kahn and mastix were all normal. The spinal fluid cell counts in these 28 cases were less than 5 in 23 cases. In 2 of the remaining 5 cases the cell count was 5, in another case it was 8. One patient's fluid contained 19 lymphocytes on admission to the hospital, and none on a subsequent examination. The last patient's cell count was 15 and 12 on 2 occasions.

*Serum Calcium* Recently it has been reported that the serum calcium level is decreased in classical typhus (24). Because of this report, serum calcium levels were obtained in 5 of our cases of murine typhus. The results were all within normal limits.

#### COMPLICATIONS

Complications occurred infrequently. Three patients contracted pneumonia, with roentgenologic evidence of consolidation. The etiology of these 3 pneumonias was not determined. One boy developed a pleural transudate, which disappeared spontaneously. Two elderly patients became uremic, one died and the other eventually improved. Two patients had acute sinusitis, otitis media occurred once. Decubitus ulcers developed in 2 patients. Delirium tremens occurred in one patient who was addicted to alcohol. Herpes labialis appeared in only 4 cases (3 per cent). The infrequency of this complication may be of some aid in differentiating typhus fever from other febrile illnesses.

#### OUTCOME

There was only one death in this series of 126 cases. This occurred in a 60-year-old colored woman. She was uremic at the time of admission to the hospital and died on the 12th day of illness. Autopsy was not obtained. It is important to note the deaths of 3 other patients in whom a clinical diagnosis of typhus fever had been made, during the 8 year period covered in this study. The clinical features in these patients were compatible with a diagnosis of typhus, but the Weil-Felix reactions were not positive up to the time of death, and autopsies were not obtained. Because of question as to the diagnosis these 3 cases were not included in the 126 cases selected for analysis, but their exclusion may indicate a falsely low case fatality rate.

#### TREATMENT

The only therapeutic indications at the present time are symptomatic and supportive measures. Parenteral fluids are beneficial, since most of the patients



are dehydrated. Other symptomatic therapy includes sedatives, analgesics and laxatives. Sulfonamides are without effect. Because atabrin has been reported to be effective in the therapy of classical typhus (23), this drug was given to 7 patients in this series, in doses of 0.3 to 0.6 gm per day. It did not appear to alter the course of the disease. Recently, we treated 3 early cases with large doses of penicillin (600,000 units per day), this also was without effect.

#### SUMMARY

The clinical features and laboratory data in 126 cases of murine typhus fever are analyzed, and criteria for the diagnosis of the disease are discussed. Other rickettsial diseases which occur in the United States are reviewed, with special reference to their nomenclature and epidemiology.

While this article was in press, another series of cases was reported from Charity Hospital in New Orleans: "Endemic (Murine) Typhus Fever. Clinical Observations of 180 Cases", B. M. Stuart and R. L. Pullen, *Ann Int Med*, **23**, 520, 1945.

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# AN INVESTIGATION OF THE EFFECTS OF RECURRENT MALARIA

## AN ORGANIC AND PSYCHOLOGICAL ANALYSIS OF 50 SOLDIERS

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*Medical Corps, A. U. S.*

### INTRODUCTION

For the past 18 months, several thousand soldiers with recurrent attacks of benign tertian malaria have been treated at this Army General Hospital. We were impressed by the constancy of certain of their complaints. Prominent among these were varying degrees of weakness and easy fatigability, intolerance to heat and sun, tenseness, headaches and gastro intestinal symptoms. These soldiers showed considerable variation in their physical reaction to the recurrent malaria. Some were markedly debilitated while the general condition of others remained good. Few significant clinical findings were ever found to account for either the complaints or the degree of debility. There was also a great difference in the manner in which the soldiers adjusted to repeated attacks of malaria. Some were able to continue full field duty, while others had to be given limited duty or were returned to the United States. Obviously, the question arose as to what organic alterations the malaria might have produced and whether they were sufficient in themselves to account for the whole clinical picture. The interplay of organic and psychological factors was recognized, but the relative proportion and importance of each was unknown. It therefore seemed of value to study the reaction of the individual as a whole to his recurrent malaria. A survey of the malarial literature, which of necessity was limited to a review of the Tropical Diseases Bulletin from 1922 to 1943, and several standard text-books on tropical diseases, while revealing a tremendous amount of work devoted to particular phases of the malaria problem, disclosed no clinical study of the total effects of recurrent malaria upon the complete individual. Additional considerations have contributed to the desire to make such an analysis. Experience taught that many soldiers have misapprehensions and ignorant fears about what recurrent malaria has done to them, and will continue to do in the future. These fears contribute to a neurotic reaction to their disease. A clarification of the total effects of malaria might be helpful in dispelling such fears. After the war the question of disability compensation will arise. Malaria will doubtless be blamed for many obscure complaints. We should have well established ideas as to what malaria can and cannot do in the way of producing permanent disability. Since the physical and emotional reaction to the disease varied so much from individual to individual, could certain broad criteria be found to aid in de-

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termining which soldiers might be most likely incapacitated by recurrent malarial infection? And further, having acquired recurrent malaria, what factors might be helpful in determining a soldier's future duty status, so that he might be used most efficiently? Finally, optimum therapy of the soldier with recurrent malaria predicates a knowledge of the total effects which the disease may produce in him.

Therefore, the study was planned to include a detailed analysis of historical and physical data, the utilization of all available pertinent laboratory techniques, as well as special consideration of psychological factors.

#### METHOD OF STUDY

Fifty soldiers who had suffered recurrent attacks of benign tertian malaria were selected. Complete blood and urine examinations were made, certain functional and metabolic studies performed as outlined in the schedule (Table 1), and fatigue tests were carried out. Consultation was had with Ophthalmological and Psychiatric specialists in every case. In certain instances, when indicated either by clinical or laboratory findings, more specialized investigations were made by the Urologist and the Otolaryngologist.

A small separate ward was devoted to the study of these fifty patients. Special personnel was selected and equipment and facilities were arranged solely for this study. The soldiers, six at a time, were admitted to the ward, and the study period extended over seven days. The reasons for this investigation and the nature of each test were carefully explained to the soldiers. It was felt that complete cooperation was given by every patient. To insure the greatest reliability of the historical data and the performance of the tests, the soldiers clearly understood that this survey would in no way influence their disposition or duty status. The studies were carried out in each case according to the schedule in Table 1. The total effect of any illness upon an individual, may be expressed in terms of physical and psychological factors. Considerable experience in the treatment of recurrent malaria here during the past eighteen months had re-emphasized the inter-relationship of these factors in our patients. It therefore seemed to us that the most fruitful way of studying the total effect of malaria upon them was to investigate and correlate the manifestations of the disease as they appeared in the patients when divided into four categories as follows:

*Group One*—Soldiers with multiple attacks of recurrent benign tertian malaria, in good physical condition, and well adjusted (14 subjects)

*Group Two*—Soldiers with multiple attacks of recurrent benign tertian malaria, in poor physical condition, but well adjusted (12 subjects)

*Group Three*—Soldiers with multiple attacks of recurrent benign tertian malaria, in poor physical condition, and badly adjusted (13 subjects)

*Group Four*—Soldiers with multiple attacks of recurrent benign tertian malaria, in good physical condition, but badly adjusted (11 subjects)

In this study the soldiers were not placed in any of these categories until after an evaluation of the history and physical examination, and a week of observation and study. The psychiatrist grouped the patients as to adjustment independently, and it is of interest that complete agreement was reached regarding

TABLE 1  
*Study Schedule*

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**Day One**

- 1) Complete history and physical examination
- 2) Intravenous glucose tolerance test
- 3) Complete urine examination
- 4) Stool examination for ova and parasites
- 5) Serological test for syphilis (Kahn)
- 6) Phenolsulphonthalein urinary excretion test

**Day Two**

- 1) Basal metabolic rate determination
- 2) Bromsulphalein liver function test
- 3) Stool examination for ova and parasites
- 4) Hines cold pressor test
- 5) Schneider Index
- 6) Running in place fatigue study
- 7) Postural hypotension study on tilt table

**Day Three**

- 1) Urinary concentration test
- 2) Stool examination for ova and parasites
- 3) Schneider Index
- 4) Running in place fatigue study
- 5) Postural hypotension study on tilt table

**Day Four**

- 1) The Kepler Power Water Test for adrenal cortical insufficiency
- 2) Electrocardiogram
- 3) Teleoroentgenogram of the chest
- 4) Schneider Index
- 5) Running in place fatigue study
- 6) Postural hypotension study on tilt table

**Day Five**

- 1) Three day salt deprivation test, for adrenal cortical insufficiency begun
- 2) Blood taken for total serum proteins with albumin globulin ratio, serum sodium, potassium and chloride
- 3) Blood taken for a complete hematological examination

**Day Six**

- 1) Basal metabolic rate determination
- 2) Complete urine examination
- 3) Psychiatric or Ophthalmological consultation
- 4) Determination of mental age by Stanford Binet and Kohs tests

**Day Seven**

- 1) Completion of the 3 day salt deprivation test
  - 2) Blood drawn for serum sodium, potassium chloride, and hematocrit
  - 3) Psychiatric or Ophthalmological consultation
  - 4) Rorschach test
-

all but three The different opinions concerning the grouping of these three cases were reconciled after discussion By the term adjustment, as used in this study, we mean the practical, effective utilization of the patient's resources in the situation at hand This practical adjustment was chosen in preference to the more indefinite term "morale" In the last analysis the evaluation of adjustment was determined by the capacity and willingness of a soldier to do his job

### HISTORY

In taking the history, an effort was made to obtain as complete a picture as possible of the soldier as an individual, in order that we might better understand his reaction to malaria Consequently, more emphasis was placed on the soldier's background and his adjustment to civilian and military life than is stressed in the usual type of medical history So that the histories would be as uniform and comparable as possible, a detailed form was designed The form, based on the usual comprehensive medical history, was amplified to include inquiry into constitutional traits, school and work record, tolerance to physical and mental strain in the past, rapidity of recovery from fatigue, and tolerance in the past to heat, sun and cold An entire section was devoted to those symptoms which have seemed to us most commonly associated with chronic malaria An attempt was made to determine whether these symptoms had ever existed in the past, to what degree, and whether they had been felt under physical or emotional stress and strain A complete malarial history and detailed weight record were obtained The historical data in the routine family and past histories and the system review revealed that there was no familial disease, and that the past general health of each soldier had been good The special data, dealing with constitutional and environmental factors and previous adjustments, is to be correlated with the patient's adjustment to recurrent attacks of malaria in a later section of the study

The fifty soldiers, with two exceptions, were members of combat divisions that had seen action, where they were heavily seeded with benign tertian malaria during a period extending roughly from October 1942 to March 1943, when they were removed for a rest period here They remained for one year until March 1944, when this study was begun During this interval attempts were made both by the hospitals and the regimental medical personnel to eliminate all those who not only as a result of their malaria, but also as a result of their emotional maladjustment, were considered no longer fit for duty in this theater of operations These were returned to the United States A further weeding out was made just prior to the division's return to action in November 1943, when those men thought unfit for combat duty were reassigned to non-combat duty in a non-malarious area This group consisted for the most part of men who had not been sufficiently ill to require disposition earlier, and in whom sufficient improvement had been anticipated to permit return to action Because of the frequency of their malarial recurrences and the development of chronic malarial symptoms this hope was not realized It was from this latter group that the patients for this study were drawn

The patients were white males, ranging in age from 21 to 32 years, with an average age of approximately 25 years. There was no significant age difference among the four groups.

**Malarial History** All of these 50 soldiers came from units heavily infected with benign tertian malaria. This malaria was characterized by moderately severe paroxysms, readily controlled by the usual forms of therapy, and by frequent and multiple recurrences which were not influenced by the type of therapy employed. Complications were infrequent. The recurrence rate observed in this Hospital during the early course of the disease was approximately 50 per cent. While in combat these soldiers were exposed to both falciparum and quartan as well as benign tertian malaria. Immediately after arrival in March 1943 *P. falciparum* parasites were found in approximately 32% of the smears at this hospital, but six months later, this strain had died out and was not found.

TABLE 2  
*Showing the patient attack rate in each group*

NUMBER OF ATTACKS	15-17	8-12	4-8	0-4	AVER AGE
Group One (Good Physical) (Good Adjustment)	5	7	2	0	10.7
Group Two (Poor Physical) (Good Adjustment)	4	7	1	0	11
Group Three (Poor Physical) (Poor Adjustment)	2	8	3	0	9.3
Group Four (Good Physical) (Poor Adjustment)	2	8	1	0	10
Totals	13	30	7	0	10

subsequently. In none of the soldiers included in this study could even a suggestive history be obtained of blackwater fever, cerebral malaria or any other serious complication of the disease. At the time of the study none of the patients had clinical evidence of acute malaria. Thick malarial smears were negative in all but two cases.

Table 2 indicates the number of attacks sustained by these 50 patients. It can be seen that there is no appreciable difference in the number of attacks occurring in the four groups. The average number of attacks per patient was ten.

**Suppressive Therapy** Fourteen of the fifty patients were receiving suppressive therapy at the time of the study. Of these, forty were taking atabrine 0.4 gram per week, and the remaining three took quinine 0.3 gram per day. Seven were receiving no therapy.

**Interval between attacks** An effort was made in each case to determine as accurately as possible the interval between attacks. Because of the large number of attacks recurring over a period of 8 to 15 months an accurate determination of this interval was not possible. It appeared, however, that early in the disease the attacks occurred at shorter intervals, approximately once a month, while as the disease progressed the interval lengthened to 6-8 weeks. The factors responsible for this change could have been either the natural course of the disease, the wider employment of suppressive therapy, or both. It was not possible to



determine what part malarial suppressive therapy, known to be effective, played in prolonging the free interval between attacks during most of the course of their disease, as it was applied inconstantly over this period. The interval between the patient's last malarial attack and the time at which these studies were made averaged six weeks. Table 3 shows this time interval as it occurred in each group, and it can be seen that there is no appreciable difference between them.

*Past Malarial Therapy* The divisions from which these patients were drawn represented the first malarial casualties which the Army treated in this theater. Consequently, the treatment extending from October 1942 to November 1943 was partly experimental, both as far as the therapy of the acute attack and suppressive measures were concerned. Irrespective of the type of therapy employed, the soldiers were treated early in each attack, and the following the first paroxysm in the great majority. The methods of therapy included the use of atabrine, quinine and plasmochin either singly or in combinations. Atabrine was the drug most commonly used. It was given in small dosage for a short period of time (1.5 grams within 5 days), small doses for long periods (2.1 grams per week for 8 weeks), in massive doses for short periods (1.5 grams in 24 hours), and other

TABLE 3

*Showing the number of weeks intervening between last attack of malaria and the performance of studies*

GROUP	ONE	TWO	THREE	FOUR	AVERAGE
Weeks	5	6	5	8	6

dosage schedules up to 6.3 grams within seven days. Some of the patients received the drug intramuscularly. Quinine was used frequently in varying dosages while the soldiers were in combat, but after reaching here only those received it who were intolerant to atabrine. Rarely quinine was used intravenously. In March 1943, shortly after arriving here, the great majority of these patients received one or two courses of plasmochin, in dosage varying from 20 to 30 mgm daily for 5 days. This type of therapy was soon discontinued because of the widespread occurrence of severe abdominal pain, nausea and vomiting which accompanied its use. In November 1943, consequent upon a directive from the Surgeon General's Office, the treatment of the acute attack was standardized to the use of atabrine in the dosage of 2.8 grams over a seven day period. While all of these methods of therapy were uniformly and equally effective in controlling the acute attack, a patient rarely having more than one paroxysm following the institution of treatment, it did not appear that one type was more effective than another in influencing the recurrent course of the disease, once the form of therapy was completed.

We have already called attention to the variable application of suppressive measures in these patients. Atabrine was used in dosages varying from 0.4 gram per week to 0.7 gram per week except in rare instances when the soldier was unable to tolerate this drug, and then quinine was substituted in dosage varying

from 0.3 to 0.6 gram per day. In the five months period from June 1943 to November 1943, the majority of these patients received no suppressive therapy. After November 1943, uniform suppressive measures were instituted, and the soldiers were given 0.4 gram of atabrine a week suppressively. Although prior to this time, the varying and inconstant employment of suppression had made it impossible to evaluate its effectiveness, following the use of this uniform regime, the rate of recurrences in this group of soldiers was markedly reduced.

*The Appearance of Symptoms* It can be seen from Table 4, that chronic symptoms made their appearance earlier in patients who were in poor physical condition at the time of this study, (Groups II and III), than they did in those patients whose physical condition remained good (Groups I and IV). Approximately 80% of the patients in the former category began having symptoms within the span of the first four attacks as contrasted to approximately 50% in the latter groups. This observation may have some prognostic value in indicating that patients who develop chronic symptoms after the first few attacks are likely to fare less well.

TABLE 4

*Showing attack following which chronic symptoms appeared*

NUMBER OF PATIENTS IN	GROUP ONE (GOOD PHYS.) (GOOD ADJ.)	GROUP TWO (POOR PHYS.) (GOOD ADJ.)	GROUP THREE (POOR PHYS.) (POOR ADJ.)	GROUP FOUR (GOOD PHYS.) (POOR ADJ.)
Attack after which symptoms appeared				
1-4	7	9	11	6
5-8	5	3	2	3
9-10	2	0	0	2

*Symptoms* Chart 1 lists the chronic symptoms most commonly mentioned by the patients, and the frequency of the occurrence of each. It should be emphasized that we are not considering the symptoms accompanying the acute attacks of malaria, but the symptoms which have been more or less constantly present between attacks for the past six to twelve months. The most common of these was weakness, present chronically in 94% of the patients. This was described variously as loss of muscular strength, easy fatigability, and lack of physical and mental energy. Because of it, the soldiers were unable to perform strenuous activity, and in some instances were unable to do even light work. Some degree of weakness had been experienced at times prior to the onset of malaria in 15 of the 50 patients, when they were subjected to either mental or physical stress. Accompanying the disease weakness was present persistently and to a much greater degree. Of the 35 patients who had never had this symptom before, all but three developed it to a considerable extent. Intolerance to heat and sun appeared in 92% of the patients. An attempt was made to distinguish the almost universal discomfort occasioned by a warm tropical climate from the more specific and intense intolerance to sun and heat which seemed to

come on following repeated attacks of malaria. Of the 39 patients who had never previously been bothered by heat or sun before their malaria, 67% had it as a definite complaint afterwards. Thirty-nine patients complained of some degree of tension, 27 of them had experienced the symptom occasionally in the past, but following the malaria it was present chronically and to a more marked degree. Although excessive sweating was prominent, its relationship to malaria was difficult to evaluate because of the climate and the almost universal presence of this symptom in the past history. Thirty-six patients never complained of

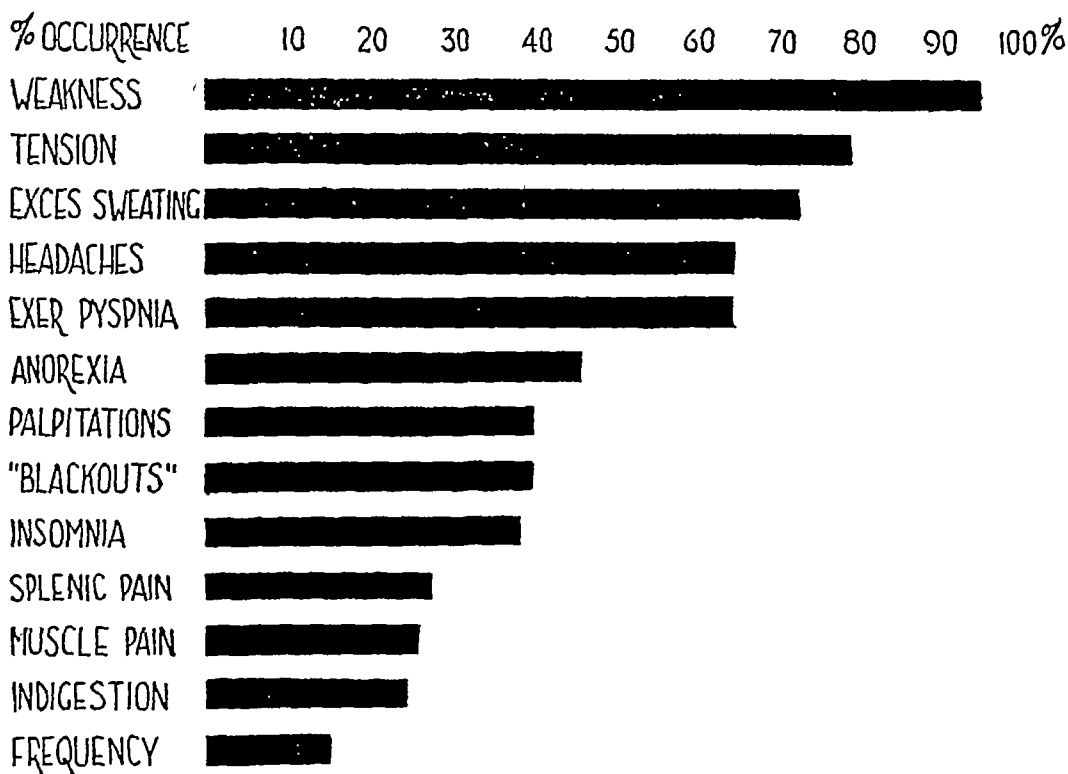


CHART 1 GRAPHIC REPRESENTATION OF THE FREQUENCY, EXPRESSED AS PERCENTAGE, WITH WHICH THESE MOST COMMONLY OCCURRING SYMPTOMS WERE CHRONICALLY COMPLAINED OF IN THIS GROUP OF 50 SOLDIERS, SUFFERING FROM TREATED BUT RECURRENT TERTIAN MALARIA

headaches prior to malaria. Of these, 26 or 70% developed chronic headaches, which varied greatly in character, were of all grades of severity, and had no particular localization. They did not simulate any specific clinical type but resembled what is usually considered under the broad heading of tension headache. It was impossible to relate these headaches definitely to either tension or to intolerance to heat or sun, because in every case but two, these three symptoms were equally prominent. Of the 42 patients who had never complained of exertional dyspnea before malaria, 60% had this symptom at the time of this study. The dyspnea described by these patients was mild to moderate in degree. It was not accompanied by the other symptoms commonly occurring with neurocirculatory asthenia. Frequently associated complaints were anorexia and insomnia in

approximately 40% of the patients, and indigestion to a lesser degree. Palpitations, described as mild to moderate cardiac consciousness after effort, were frequently associated with a tendency to dizziness and "blackout." This was not a true vertigo, but was described variously as a momentary sense of instability or faintness, at times with spots before the eyes, most often apparent on assuming the erect posture. Pain referred to the splenic area occurring chronically between attacks, usually during physical exertion, was complained of by 27% of the patients. While skeletal and muscle pains were principal complaints during acute attacks of malaria, they were insignificant at other times. Other symptoms including frequency, dysuria, nocturia, diarrhoea, constipation, and salt craving, were specifically inquired about and found to be of little importance. Their libido was normal.

TABLE 5  
*Showing the weight loss in each group*

NUMBER OF PATIENTS IN	GROUP ONE (GOOD PHYS.) (GOOD ADJ.)	GROUP TWO (POOR PHYS.) (GOOD ADJ.)	GROUP THREE (POOR PHYS.) (POOR ADJ.)	GROUP FOUR (GOOD PHYS.) (POOR ADJ.)
Pounds lost				
20-30	2	5	8	2
10-20	6	4	4	4
5-10	3	2	0	3
0-5	3	1	1	2
Average weight loss	10.6	17.3	20.6	11.3

The significance of these symptoms, their sources in the psychological or organic fields, or both, and their relationships to the group divisions, will be discussed later, after the background of objective physical, laboratory and special test data has been presented.

#### PHYSICAL EXAMINATION

A complete physical examination including a rectal and neurological was done, and the findings recorded on a standard form. In addition, every soldier was observed by all of us with the intension of reaching a common opinion as to his general physical status upon which in part his group classification depended. No physical abnormalities were discovered in these examinations other than weight loss, debility, and in a few cases, a palpable liver and spleen. Table 5 shows the weight loss which occurred in each group.

In every instance inquiry was made of the soldier's weight at the time of induction, at the port of embarkation, and just prior to the onset of malaria. The weight loss recorded represents only that occurring during the course of the malarial infection up to the time of the present study. How much of this loss can be attributed solely to malaria, and how much is due to other factors, such as combat, tropical life, etc., can only be surmised. Once the stresses of combat existence had been removed, the fact that most of these individuals failed to re-

gain their weight, over a period of 9 months to a year in a rest area, suggested that the prime cause of their inability to gain was the recurrent malaria. Their weight loss was considerably in excess of that observed in other soldiers resident in this area for 22 months but who had had no malaria. It is apparent that soldiers placed in groups II and III on the basis of poor physical condition would have the greatest weight loss. The degree of debility and the nutritional status paralleled the weight loss. Of the fifty soldiers, four had palpable livers and spleens, three others palpable spleens, and one other only a palpable liver. These organs extended one to two centimeters below the costal margin, and were slightly tender. The splenic and hepatic enlargement showed no group predominance. Of the 14 patients with splenic pain, only 2 had palpable spleens.

#### LABORATORY DATA

*Hematologic Studies* A transient anemia is described as a not uncommon accompaniment of the acute malaria attack, but does not usually persist in the interval between attacks in the chronic recurrent form of the disease, when adequately treated (1, 2). A complete hematological study was made on each patient and the results which were essentially normal are shown in Tables 6 to 13 inclusive. All determinations were done on oxalated venous blood using the Wintrobe oxalate mixture (3). Blood smears were drawn with capillary blood. Only one soldier had anemia, the average red blood cell count being 5,080,000 per cmm and the hemoglobin averaging 15.8 grams per 100 ml (using the Fisher Electro-Hemometer standardized so that 15.6 grams equals 100%). This one soldier had a mild normocytic, normochromic anemia which responded rapidly to a short course of iron therapy. The average white blood cell count was normal. It can be seen from Table 10, that there was a moderate relative lymphocytosis. This lymphocytosis cannot be attributed directly to the malaria, because it was the common experience in this hospital laboratory to find an increase in the lymphocyte count in apparently healthy individuals who had never had malaria. This has been reported elsewhere (4) as occurring in individuals resident in the tropics. Three patients showed an eosinophilia of from 12 to 20%. In two of these intestinal parasites were found in stool examinations, and the third who had been treated for hookworm one month previously, had nine negative stool examinations at the time of the study. All were asymptomatic. The sedimentation rate was determined and corrected according to the Wintrobe technique (3), in which the normal range is considered zero to ten millimeters per hour. All soldiers who had a sedimentation rate of over 12 were studied for a focus of infection by the urological, otolaryngological and dental consultants in an attempt to determine whether the elevation was due to the malaria per se or to some other cause. There were eight such cases. Of these one had an external otitis, another an infected tooth and the third hookworm infestation. In this latter patient the sedimentation rate returned to normal after treatment. In the remaining five no cause for the elevation of the sedimentation rates was found, and we were forced to the conclusion that either they belonged to the group of unexplainable elevations, or that the elevations were related to the

chronic malaria It should be noted that five of these eight cases were in group I (those in good physical condition)

The icterus index was determined by comparing the blood serum with a standard solution of potassium dichromate The normal range was considered to be four to nine units The average icterus index was 5.7 and there was no significant elevation in any instance

Since an increase of the fragility of the red blood cells has been reported in uncomplicated malaria (5), we were interested in studying this factor in our

TABLE 6

*Showing the average red blood cell count in each group, the range, and average for all fifty patients*

GROUP	AVERAGE RBC PER CMM.	RANGE OF RBC PER CMM
Group One (Good Physical) (Good Adjustment)	4,900,000	4,460,000 to 5,650,000
Group Two (Poor Physical) (Good Adjustment)	5,050,000	4,180,000 to 5,820,000
Group Three (Poor Physical) (Poor Adjustment)	5,140,000	4,170,000 to 6,100,000
Group Four (Good Physical) (Poor Adjustment)	5,220,000	4,560,000 to 6,860,000
Average	5,080,000	

TABLE 7

*Showing the average hemoglobin determination in each group, the range, and average for all fifty patients*

GROUP	AVERAGE HEMOGLOBIN	RANGE OF HEMOGLOBIN
	Grams/100 ml	Grams/100 ml
Group One (Good Physical) (Good Adjustment)	15.5	13.9 to 18.2
Group Two (Poor Physical) (Good Adjustment)	16.2	14.5 to 18.2
Group Three (Poor Physical) (Poor Adjustment)	15.7	13.4 to 18.0
Group Four (Good Physical) (Poor Adjustment)	16.0	14.4 to 18.5
Average	15.8	

patients The erythrocyte fragility was tested by resistance to hypotonic salt solution according to the technique described by Wintrobe (3) By this method hemolysis normally begins at 0.45% to 0.30% NaCl, and is complete at 0.33% to 0.30% NaCl The test was controlled in each instance with erythrocytes from different normal individuals who had never had malaria Although as shown in Table 13, hemolysis in these soldiers began in some instances at a higher concentration of NaCl than Wintrobe's normal, the fact that in each instance they corresponded so closely to the normal controls seemed more significant We believe that the difference between his results and ours was one of technique, and that our values represented a normal fragility in these patients Furthermore, other fragility studies done in this hospital laboratory on 30 additional patients with recurrent benign tertian malaria, showed normal fragility (6)

*Serological Test for Syphilis* It is a well known fact, that false positive serological tests for syphilis occur frequently in acute malaria In the acute attack

TABLE 8

*Showing the average hematocrit in each group, the range and the average in all fifty patients*

GROUP	AVERAGE HEMATOCRIT	RANGE
	cc /100 cc	cc /100 cc
Group One (Good Physical) (Good Adjustment)	44	41 to 51
Group Two (Poor Physical) (Good Adjustment)	45	36 to 50
Group Three (Poor Physical) (Poor Adjustment)	46	39 to 52
Group Four (Good Physical) (Poor Adjustment)	43	44 to 52
Average	44	

TABLE 9

*Showing the average white blood cell count in each group, the range, and average for all fifty patients*

GROUP	AVERAGE WBC/CM <sup>3</sup>	RANGE WBC/CM <sup>3</sup>
Group One (Good Physical) (Good Adjustment)	6500	3700 to 8900
Group Two (Poor Physical) (Good Adjustment)	6000	4900 to 8000
Group Three (Poor Physical) (Poor Adjustment)	6600	3900 to 9500
Group Four (Good Physical) (Poor Adjustment)	5400	4200 to 10,000
Average	6200	

TABLE 10

*Showing the average percentage of the various white blood cell forms found in each group, the range, and average for all fifty patients*

GROUP	% OF POLYS	RANGE % POLYS	% OF LYMPHS	RANGE % LYMPHS	% OF MONOS	RANGE % MONOS	% OF EOSINES	RANGE % EOSINS	% OF BAS
Group One (Good Phys ) (Good Adj )	49	36-66	55	30-58	3	0-28	4	0-12	0 3
Group Two (Poor Phys ) (Good Adj )	56	39-70	41	24-56	0 5	0-7	3	0-12	0 3
Group Three (Poor Phys ) (Poor Adj )	49	36-68	46	26-61	2	0-4	2	0-8	0 2
Group Four (Good Phys ) (Poor Adj )	49	27-58	43	28-52	1	0-6	4	0-20	0 5
Average	50		46		1 6		3 2		0 3

they have been reported in as high as 100% of the cases (7) Positive tests have been known to persist for as long as 3 months and rarely 6 months after the termination of the acute attack (8) However, most tests are said to be negative

four weeks after the subsidence of fever (9) The highest percentage of positives is said to occur 15 to 21 days after the onset of the febrile period (2), (9) In this hospital there were 141 or 15.6% positive Kahn tests out of a series of 900 cases

TABLE 11

*Showing the average sedimentation rate in each group, the range, and average for all fifty patients*

GROUP	AVERAGE SED RATE	RANGE
	mm./hr	mm./hr
Group One (Good Physical) (Good Adjustment)	18	6 to 24
Group Two (Poor Physical) (Good Adjustment)	10	5 to 23
Group Three (Poor Physical) (Poor Adjustment)	5	3 to 10
Group Four (Good Physical) (Poor Adjustment)	12	6 to 35
Average	10	

TABLE 12

*Showing the average icterus index in each group, the range, and the average in all fifty patients*

GROUP	AVERAGE ICTERUS INDEX	RANGE
Group One (Good Physical) (Good Adjustment)	6.2	5 to 11
Group Two (Poor Physical) (Good Adjustment)	5.8	6 to 8
Group Three (Poor Physical) (Poor Adjustment)	5.3	4 to 8
Group Four (Good Physical) (Poor Adjustment)	5.7	5 to 13
Average	5.7	

TABLE 13

*Showing the average red blood cell fragility, the range in each group, and the average in all fifty patients*

GROUP	AVERAGE FRAGILITY—% NaCl BEGINNING HEMOLYSIS—COMPLETE HEMOLYSIS	RANGE—% NaCl BEGINNING HEMOLYSIS—COMPLETE HEMOLYSIS
Group One (Good Physical) (Good Adjustment)	0.48—0.34	0.51—0.30
Group Two (Poor Physical) (Good Adjustment)	0.47—0.33	0.54—0.30
Group Three (Poor Physical) (Poor Adjustment)	0.46—0.33	0.57—0.30
Group Four (Good Physical) (Poor Adjustment)	0.48—0.34	0.57—0.30
Average	0.47—0.33	

of benign tertian malaria Eagle et al, using the spirochaetal complement-fixation test, report a high degree of false positive reactions (10) A standard serum Kahn test (11) was done with antigen supplied by the Army Medical School on each patient The tests were all negative.



*Stool Examinations* At least three stool examinations were performed on each patient for ova and parasites, using the zinc sulfate centrifugal flotation technique (11) This was done in order to rule out intestinal parasites as a concomitant cause of debility Only three of the fifty patients were found to have intestinal parasites In two of these *Necator Americanus*, and in the third *Trichuris trichiura* were identified These three patients were asymptomatic

*Renal Studies* Renal damage due to malaria has been reported as far back as 1897 by Manson (1) Its occurrence has been most often noted in chronic recurring, inadequately treated malaria, principally of the quartan type, but also in falciparum and tertian infections (12-15) The frequency of albuminuria without other objective evidence of renal damage, in both acute and chronic malaria, has been noted (16) Various pathological lesions, from cloudy swelling to those commonly associated with glomerular nephritis or nephrosis, have been described (1, 14, 15) It has been reported that quinine is not contraindicated in malarial nephritis, and may be particularly beneficial (14, 15, 17) Because of

TABLE 14

*Showing the average specific gravity and the range for each group achieved at the completion of the Urine Concentration Test*

GROUP	AVERAGE SPECIFIC GRAVITY	RANGE
Group One (Good Physical) (Good Adjustment)	1 025	1 022 to 1 030
Group Two (Poor Physical) (Good Adjustment)	1 026	1 021 to 1 035
Group Three (Poor Physical) (Poor Adjustment)	1 024	1 020 to 1 026
Group Four (Good Physical) (Poor Adjustment)	1 024	1 020 to 1 030
Average	1 025	

these reports the following studies were done In each instance two complete urine examinations including microscopic study of centrifuged sediment were performed These were normal in every case Urine concentration tests were done as follows Fluid at the 4 30 P M evening meal was limited to 200 cc, and no fluid or food was permitted thereafter until the completion of the test The patient was made to void at 10 P M, and this specimen was discarded Subsequent specimens of urine were collected at 8, 9, and 10 A M the following morning, and the specific gravity of each specimen determined The results are noted in Table 14 The average concentration reached was a specific gravity of 1 025, which is normal according to the standard of Fishberg (18) A two hour phenol-sulphonthalein urinary excretion test was performed Specimens were collected at 15 minutes, one-half hour, and two hours after the injection of the dye Fluids were forced to maintain an adequate urine output A normal 15 minute excretion was obtained in all but three of the patients These excreted only seventeen per cent in the first fifteen minutes as compared with the so-called minimal normal of 25% In all the patients the 30 minute and total excretions of the dye were normal (Table 15)

The results of these renal studies led us to believe the malaria had produced no kidney damage or impairment of function in these fifty patients

**Liver Function Tests** Enlargement of the liver is a frequent finding in acute malaria. Impairment of liver function in therapeutic malaria with *P. vivax* has been reported to persist up to 3 to 6 weeks following termination of the infection (19, 20). Evidence of liver damage has also been reported in naturally occurring acute benign tertian and falciparum infections (21, 22). The reversibility of these changes, following treatment, has been emphasized by Manson (1). In chronic untreated malaria it is well known that permanent liver damage occurs, tending to progress to cirrhosis (1, 23). As a result of the frequency with which we observed liver enlargement in acute malaria, and the implications of these reports, and the reported suspected impairment of liver function due to atabrine administration over a prolonged period (2), liver function was studied. The limited significance of any one or more liver function tests is recognized. Because of the scarcity of materials it was necessary to confine ourselves to the use of the

TABLE 15

Showing the average two hour excretion of phenolsulphonphthalein in each group, the range, and the average excretion for all 60 patients

GROUP	AVERAGE PER % 2 HR. EXCRE- TION	RANGE %
Group One (Good Physical) (Good Adjustment)	62	45 to 75
Group Two (Poor Physical) (Good Adjustment)	63	55 to 71
Group Three (Poor Physical) (Poor Adjustment)	56	45 to 77
Group Four (Good Physical) (Poor Adjustment)	62	55 to 73
Average	61%	

bromsulphalein dye excretion test (2 mgm. per kilogram of body weight) in forty of the patients, and the intravenous hippuric acid test (1.77 gm. sodium benzoate) in the remaining ten cases. In addition the total serum proteins with protein partition and the icterus index were determined. The bromsulphalein and hippuric acid tests were normal in every instance. The total serum protein determinations and the albumin and globulin ratios were normal throughout as shown in Table 16. The icterus index has already been described as normal. Liver function, therefore, as evaluated by the methods employed, was normal in all patients.

**The Basal Metabolic Rate** Two or more basal metabolic rate determinations were done on each individual, and the average for each group is shown in Table 17. The average for the fifty patients was minus 7.9 per cent of normal. It can be seen that the great majority of patients had a basal metabolic rate in the range of minus twenty to plus five per cent of normal. The basal metabolism of normal white persons in tropical climates is said to be reduced (24, 25). The experience at this hospital, (Hospital X, table 17), and that of another general hospital here, (Hospital Y) (26), employing a different type of a machine, tend to

substantiate this fact. A communication from another hospital (Hospital Z) (27), confirms this tendency to a lowered basal metabolism. Table 17 shows the close correlation between 180 basal metabolic rate determinations done on normal white individuals resident in the tropics, and the rates found in our fifty malarial patients.

*The Adrenal Glands* Degenerative lesions in the adrenal glands associated with muscular weakness, asthenia, pigmentation and hypotension have been described as occurring in chronic infections due to *P. falciparum*, as well as to *P. vivax* (1), (2), (28), (29). It therefore seemed worthwhile to investigate adrenal cortical function in these patients, particularly since asthenia was such a common and prominent symptom. Although none of the subjects presented clinical

TABLE 16

*Showing the serum proteins and the serum albumin and globulin values determined in 50 malarial patients*

GROUP	TOTAL PROTEINS	RANGE	ALBUMIN	RANGE	GLOBULIN	RANGE
	gms / 100 cc	gms / 100 cc	gms / 100 cc	gms / 100 cc	gms / 100 cc	gms / 100 cc
Group One (Good Phys ) (Good Adj )	7.8	7.2 to 8.3	4.0	3.1 to 4.9	3.7	3.0 to 4.6
Group Two (Poor Phys ) (Good Adj )	7.6	6.7 to 8.3	4.3	3.8 to 5.0	3.2	2.8 to 4.7
Group Three (Poor Phys ) (Poor Adj )	7.4	6.4 to 8.4	4.3	3.4 to 5.0	3.3	2.4 to 3.9
Group Four (Good Phys ) (Poor Adj )	8.0	7.1 to 9.0	4.5	4.0 to 5.0	3.5	2.8 to 4.4
Average	7.7		4.2		3.4	

Serum Protein determination by Andersch and Gibson's modification of method of Wu and Ling (11)

evidence of Addison's Disease the possibility of a subclinical adrenal cortical insufficiency was still present. It has been suggested that some patients suffering from asthenia and exhaustion may temporarily show signs of adrenal cortical insufficiency (30). The tests chosen for our investigation were the Kepler-Power water test, (31), a three day salt deprivation test, and an intravenous glucose tolerance test.

The Kepler-Power water test is based on the observation that following the rapid intake of a considerable quantity of water, patients having Addison's disease usually do not experience a normal diuresis. The technique used was that described by Robinson, Power and Kepler, Procedure 1, (31). Forty-six of the fifty malarial subjects had a negative test. The test was positive in 4 cases, even when repeated. However, these individuals showed no other clinical or laboratory evidence of Addison's disease.

When this study was begun, the details of the exact routine of the Cutler-Power-Wilder Chloride Excretion Test for adrenal cortical insufficiency were

not available (32) Our patients were placed on a salt deprivation diet for 3 days This diet contained 0.93 gm of chloride ion, 0.59 gm of sodium ion, and 4.2 gm of potassium No additional potassium was given and fluids were allowed ad lib Blood pressure determinations were made each morning under basal conditions and the patients were then weighed On the first morning of the test, blood samples were taken for determination of hematocrit and serum chloride, sodium and potassium On the last morning of the test, these blood determinations were repeated Urine was collected from 8 A.M. to 12 noon of the third

TABLE 17

*Showing the basal metabolic rate determinations made upon fifty patients with recurrent malaria and upon one hundred and eighty subjects resident in a tropical climate*

RANGE OF BMR	MALARIAL SUBJECTS					NORMAL SUBJECTS			
	Group one (good phys. good adj.)	Group two (poor phys. good adj.)	Group three (poor phys. poor adj.)	Group four (good phys. poor adj.)	Total cases	Cases X hospital	Cases Y hospital	Cases Z hospital	Total cases
+30 to +20	0	0	1	0	1	1	3	0	4
+10 to +10	2	1	0	0	3	6	12	0	18
+9 to +5	0	0	0	2	2	1	8	4	13
+4 to 0	1	0	2	2	5	2	10	3	15
0 to -5	3	2	2	2	9	5	10	4	28
-6 to -10	2	3	2	0	7	4	18	4	26
-11 to -15	1	3	1	3	8	5	17	5	27
-16 to -20	3	3	3	0	9	4	14	4	22
-21 to -25	2	0	2	2	6	3	8	2	13
-26 to -30	0	0	0	0	0	1	8	1	10
-31 to -40	0	0	0	0	0	0	4	0	4
Total cases	14	12	13	11	50	32	121	27	180
Average BMR	-8.0	-9.0	-8.0	-6.6	-7.9	-5.3	-7.4	-8.0	-6.9
Range	Of the malarial subjects -23 to +20					Of the normal subjects -30 to +26			

day, and the concentration of chloride excreted during this test period determined Particular attention throughout the test was given to the observation of signs and symptoms suggesting adrenal cortical insufficiency None of these developed The asthenia persistently present to a variable degree in most of the patients was not in any instance accentuated Table 18 summarizes the laboratory data in the 50 malarial patients and in 34 normal controls This group of controls was thought necessary because the test used differed from the standard Power Wilder Test It can be seen that the mean value for the urinary chloride concentration during the 4 hour test period was within the so-called normal limits of the Cutler test, below 225 mgm %, both in the patients and the controls The high values of urinary chloride concentration in some of the patients which resulted in such a wide range were accompanied by a low urinary

TABLE 18  
Showing the results of the 3 Day Salt Deprivation Test on the 50 malarial patients and 34 normal controls

DETERMINATION	GROUP ONE		GROUP TWO		GROUP THREE		GROUP FOUR		ALL 50 PTS		34 NORMAL CONTROLS	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Test period urinary volume (cc)	273	45 to 700	310	65 to 825	336	75 to 820	162	60 to 400	270	45 to 825	430	50 to 1200
Test period conc urinary chloride (mgm/100 cc) exp as chloride	222	5 to 516	156	15 to 495	198	40 to 490	199	51 to 305	194	5 to 516	170	35 to 507
Test period total urinary chloride (mgm)	331	35 to 670	312	60 to 660	433	236 to 784	253	110 to 410	332	35 to 784	410	114 to 1344
Blood pressure prior to test	108	98-130	103	86-110	104	90-110	107	100-116	106	86-130	102	90-130
	68	50-80	62	50-80	67	58-80	68	60-78	66	50-80	72	50-95
Blood pressure at end of test	105	98-110	101	95-110	106	100-116	104	100-110	104	95-116	103	90-120
	61	52-78	66	55-74	71	60-80	70	64-82	67	52-82	73	60-85
Weight loss during test (pounds)	2	+2 to -3	2	+1 to -6	0.8	+1 to -3	1	+6 to -6	1.5	+6 to -6	1.9	+1 to -5
Rise of hematocrit during test (mm)	2	-1 to +6	0	-3 to +2	1	-4 to +2	0	-4 to +2	0.7	-4 to +6	1.9	-1 to +6
Blood serum sodium first test day (mgm/100 cc)	341	318 to 430	331	303 to 342	316	290 to 338	334	302 to 387	330	290 to 430	354	302 to 390
Blood serum sodium third test day (mgm/100 cc)	327	280 to 368	319	294 to 343	321	289 to 348	324	298 to 361	331	280 to 368	347	305 to 392
Blood serum potassium first test day (mgm/100 cc)	18.7	16.2 to 22.2	18.5	14.2 to 22.7	19.5	15.5 to 24.2	19.1	15.5 to 21.8	19	14.2 to 24.2	18.6	14.8 to 24.8
Blood serum potassium third test day (mgm/100 cc)	19.7	15.1 to 24.3	20.5	16.5 to 25.2	19.8	15.1 to 24.2	19.5	16.8 to 22.2	19.9	15.1 to 25.2	20.5	15.4 to 27.3

Blood serum chloride first test day (mgm./100 cc.)	362	338 to 373	368	350 to 375	372	360 to 384	358	356 to 375	305	336 to 384	364	343 to 401
exp as chloride												
Blood serum chloride third test day (mgm./100 cc.)	360	350 to 375	360	345 to 374	365	350 to 375	350	294 to 373	350	294 to 375	358	338 to 371
exp as chloride												

*Methods used in the chemical determinations*

Urinary chloride—Volhard Arnold (32)

Serum sodium —Weinbach's modification of Butler and Tutthill's method (32)

Serum potassium—Bren and Caebler (32)

Serum chloride —Whitehorn (32)

volume. Consequently, the total chloride lost was not great. It should be noted again that our patients were on a free fluid intake in contrast to the forced fluid regime of the Cutler Test. Under such circumstances, some normal individuals taking less fluids than others would be expected to excrete a more concentrated urine. Ten of the 50 malarial patients and 8 of the control group had high urinary chloride concentrations. Therefore, in these eighteen subjects, no definite conclusions could be reached regarding the significance of high urinary chloride concentration as a reflection of border-line adrenal cortical insufficiency. The four patients mentioned above, who showed a positive result in the Kepler-Power water test had a normal urinary chloride excretion. It should be empha-

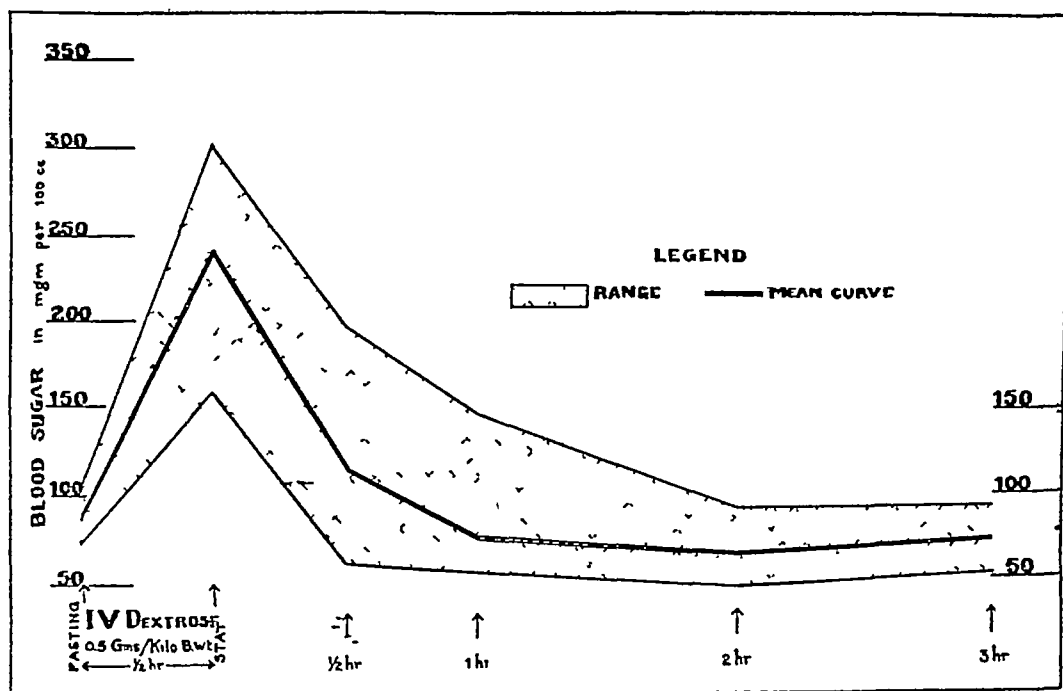


CHART 2 GRAPHIC REPRESENTATION OF THE RESULTS OF INTRAVENOUS GLUCOSE TOLERANCE TESTS DONE ON 50 SUBJECTS WITH CHRONIC RECURRENT, BUT TREATED, BENIGN TERTIAN MALARIA

sized that the changes in blood pressure, the degree of hemoconcentration, the loss of body weight and general systemic reaction during the test, did not suggest adrenal cortical insufficiency in any of the 84 subjects studied. Furthermore, the serum sodium potassium and sodium chloride determinations made on the first and third test days, were well within normal limits.

An intravenous glucose tolerance test was done on each of the malarial patients. A fasting blood sugar was obtained, using venous blood, and then 0.5 gram of glucose per kilogram of body weight, in a 20% solution of distilled water, was given over a period of 30 minutes. Immediately at the end of the infusion, and at one half, one, two, and three hours, samples of venous blood were taken for blood sugar determinations. Chart 2 shows a normal tolerance curve in every

instance None of the patients showed evidence of a hypoglycemic reaction, which is one manifestation of adrenal insufficiency

These tests indicated that the varying degrees of asthenia manifested by these patients were not related to adrenal cortical insufficiency

*Ophthalmological Examination* The fifty patients were given an eye examination by the Chief of the Ophthalmological Service of this hospital This examination consisted of visual acuity determination, refraction under homatropine where necessary, external examination, fundus examination under full dilatation, and visual field test, both central and peripheral, on the Ferree-Rand simplified perimeter

In forty of the fifty patients the eyes were normal Five were normal except for a refractive error, which was properly corrected by their present glasses Three patients showed poor convergence with a N.P.C. of 10 cm in two cases, and 16 cm in the third This might conceivably be the result of general debility, but this percentage of poor convergence (6%), does not exceed the 7.7% found in the outpatient records of soldiers who have been stationed in the tropics for long periods, and cannot be said to be the result of their repeated attacks of malaria One patient showed an amblyopia ex anopsia which had been present all his life The remaining patient showed a slight concentric constriction (5-10°) of the right peripheral field The left peripheral field and the central fields of both eyes were entirely normal, as were visual acuity and fundus examination of both eyes No cause for this constriction was found In summary, not one of the 50 malarial patients showed any eye findings definitely attributable to the malaria This is in accord with a survey conducted on the eyes of over two hundred soldiers examined during an acute attack of benign tertian malaria in this General Hospital This has been reported to the Surgeon General's Office

Bothman, in a special article on the eye complications in malaria in the Year Book of Eye, Ear, Nose and Throat, 1943, noted that tertian and quartan forms may involve the cornea (herpetic keratitis), while the aestivo-autumnal form may involve choroid, retina, optic nerve, and cornea to cause almost every eye condition possible None of these lesions were found in this series of cases, which however, were all treated benign tertian malaria

*Cardiovascular Studies* Varying degrees and types of pathological alteration have been noted in the heart accompanying severe fulminating and chronically untreated malaria (1, 34) In some instances these changes are reflected in the electrocardiogram. Manson has suggested that individuals with valvular disease of the heart, whether compensated or not, should be considered unsuitable for residence in malarial countries Although all of our patients presented an entirely normal clinical cardiac picture, an electrocardiogram and teleoroentgenogram of the chest was done in each case, in the chance they might reveal abnormalities otherwise inapparent

*Teleoroentgenograms* Teleoroentgenograms of the chest showed the heart and lungs to be normal in all of the subjects.

*Electrocardiograms* In taking the electrocardiograms, a General Electric Portable Machine was used Good standardization and constant timing was



maintained. The three standard leads and a single chest lead, 4F, were taken on each patient in the prone position. All of the fifty tracings were within normal limits. A short discussion of some of the normal variations and Table 19, showing some of the routine measurements, have been included. No gross abnormalities in rate or rhythm were encountered. A "P" wave voltage of less than 0.7 mm. has been described as suggesting a state of "poor nutrition" of the auricles. This occurred in either or both of leads 1 and 3 in 80% of the subjects, but in only 10% in lead 2. There was no reason to suspect "poor nutrition" of the auricles in these cases. It was considered a variation within normal limits. One subject had a notched "P" wave in lead 2, and three had inverted "P" waves in lead 3. Neither this variation nor others mentioned were found in the few individuals receiving suppressive daily doses of 0.3 to 0.6 gm. of quinine. The P-R interval was within normal limits in every case. An insignificantly small "Q" wave (less than 25% of the major deflection in lead 3, less than 20% in lead 2, and less than 15% in lead 1) was present in 38% of the cases. Twenty per cent of the subjects had such insignificant "Q" waves in both leads 2 and 3, 8% in lead 1, 4% in lead 2 alone, and 6% in lead 3 alone. No "Q" waves were noted in lead 4F in any of the subjects. The "QRS" complexes were normal in axis, voltage and contour. One subject had left axis deviation, without any other abnormalities in the tracing, cardiac enlargement, unusual position of the heart or elevation in blood pressure. The duration of the "QRS" complex was within normal limits in all subjects. The "T" waves were not remarkable. In lead 3 it was biphasic in 8%, isoelectric in 4%, and inverted in 4%. Elsewhere it was upright and of normal amplitude. Lead 4F in no case was remarkable.

#### FATIGUE STUDIES

Two of the most obvious manifestations of chronic malaria in these soldiers were weakness and easy fatigability. It therefore seemed desirable to measure these factors in an objective way, if possible. The complex nature of fatigue and the marked difficulties in its measurements were quite apparent, and have been reported in the literature in detail (35). Fatigue may have a physiological, chemical, or psychological origin, and may manifest itself in several ways, among these being muscular weakness, lack of energy, nervous tension, and mental apathy. The origins and the manifestations of fatigue are so closely interrelated that it is impossible to divorce one from the other. There are many different ways of measuring these manifestations, such as standard exercise tests, ergometer readings, utilization of oxygen under controlled exercise, kymograms, mental concentration tests, and so forth. Each of these measures only an isolated phase of fatigue, and hence none of them give a complete evaluation of the fatigue state.

In our patients some of the components of fatigue were manifested by complaints of exertional dyspnea, tachycardia and palpitations under varying degrees of physical and mental stress, and by a subjective sense of weakness. We therefore selected as a simple and objective way of measuring and comparing these manifestations, a standardized running in place test and determination of the Schneider Index. In these tests the cardiovascular response to a fixed effort is

TABLE 19  
Electrocardiographic Findings

GROUP	DATE	RHYTHM	P1	P2	P3	P-R	Q	AXIS	CONT	DDR	V1	V2	V3	T1	T2	T3	QAP	T
			mm.	mm.	mm.	sec.				sec	mm.	mm.	mm.					mm.
1	L 60 H 100	Reg	0.5 1.0	0.5 2.0	0.5 1.0	0.12 0.20	*	Nor	Nor	0.02 0.08	2 12	7 13	1 15	1.0 5.0	0.5 4.0	0.5 2.0	0	2.0 5.0
AV	76		0.7	1.5	0.5	0.16				0.04	6	11	7	2.2	2.5	1.0		4.0
2	L 60 H 96	Reg	0.5 1.0	1.0 4.0	0.5 2.0	0.14 0.18	*	Nor	Nor	0.04 0.03	2 8	10 17	2 15	1.0 3.0	2.0 4.0	0.5 2.0	0	1.0 7.0
AV	74		0.6	1.5	1.0	0.16				0.07	4	12	10	2.0	3.0	1.3		4.0
3	L 60 H 100	Reg	0.5 1.0	0.5 1.5	0.5 1.0	0.12 0.18	*	Nor	Nor	0.03 0.03	2 15	6 14	1 14	1.0 4.0	1.5 4.0	0.5 2.0	0	1.0 14.0
AV	77		0.7	1.0	0.7	0.16				0.04	5	10	6	2.0	3.0	1.0		4.0
4	L 72 H 100	Reg	0.5 2.5	0.5 3.5	0.5 1.0	0.14 0.18	*	Nor	Nor	0.03 0.08	5 10	5 20	3 15	1.5 3.0	2.0 4.0	1.0 2.5	0	1.0 7.0
AV	84		1.0	1.6	0.8	0.16				0.05	6	11	6	2.0	3.0	1.0		4.0

L—low value

H—high value

AV—average

V—voltage in leads I, II, III

\*—Insignificant Q waves were noted in leads I, II, III (see discussion)

Cont—contour

Dur sec—duration in seconds

used as a measurement of body economy In addition, the question of apathy as a manifestation of psychological fatigue was investigated by the psychiatrist using the Rorschach Test

One hundred soldiers from our hospital detachment, who had never had malaria, were used as controls Their average age was 26.7 years, which is comparable to the age of the patients studied In order to bring out what part, if any, chronic malaria alone played in the development of these manifestations of fatigue, the control subjects were selected so that the effects of long stay in the tropics, maladjustment, and good or poor physical condition might be evaluated as well as possible It was apparent that the stresses and strains inherent in the life of a combat soldier, to which the malarial patients had been exposed 9 months to a year prior to the study, presented a fatigue factor that could not be controlled Unfortunately, an adequate supply of combat soldiers who had not had malaria was not available, and the controls used were selected from our hospital detachment The one hundred controls were chosen as follows

*Group (A)*—Thirty-eight soldiers who were in good physical condition, and well adjusted, who had been overseas in the South Pacific Area 22 months

*Group (B)*—Thirty-seven soldiers in good physical condition, well adjusted, who had only been overseas in this area for approximately two months

*Group (C)*—Fifteen soldiers in good physical condition, poorly adjusted, who had been overseas in this area 22 months

*Group (D)*—Ten soldiers in poor physical condition and poorly adjusted, who had been overseas in this area 22 months

These same groups of controls were employed in the other fatigue studies, with the exception of the Rorschach Test

That particular phase of the lability of the autonomic nervous system, which is measured by the Hines Cold Pressor Test (36), was studied

*Running In Place Test* This test was performed by having the soldier, clad in pajamas and Army shoes, run in place for one minute, at the approximate rate of 170 steps per minute During the running period each soldier was coached to raise his knees to at least the level of the mid thigh to assure as much uniformity as possible Before the test was begun, pulse, blood pressure and respirations were taken with the patients seated, and these determinations were then repeated, also with the patients seated, immediately at the conclusion of the running, and at periods of 1½, 3, 5, and 10 minutes afterwards Timing was done with a stop watch This test was done daily on each soldier for three successive days The same test was done three times on the one hundred controls When the three running tests had been completed on each individual, the figures obtained were graphed on a standard form which showed the relationships of the component parts of the test By use of these graphs, correlation of the successive tests done on an individual, as well as comparison with any other individual, was possible It was found that the similarity in both pattern and degree of response from test to test justified the determination of a mean value for each component in the three successive tests, and it was this mean which was used as a comparison between individual responses In order to compare the group

differences, the individual means were then plotted on a master chart and the average for each group determined, and the pattern of response represented graphically. It can be seen from Chart 3 how very similar in both degree and pattern were the means for the four groups of malarial patients. The results of the controls were treated similarly, and the means are shown in Chart 4. The response to the test in the four groups of controls was quite uniform. The small dots in both charts represent the individual means, and it can be seen that there

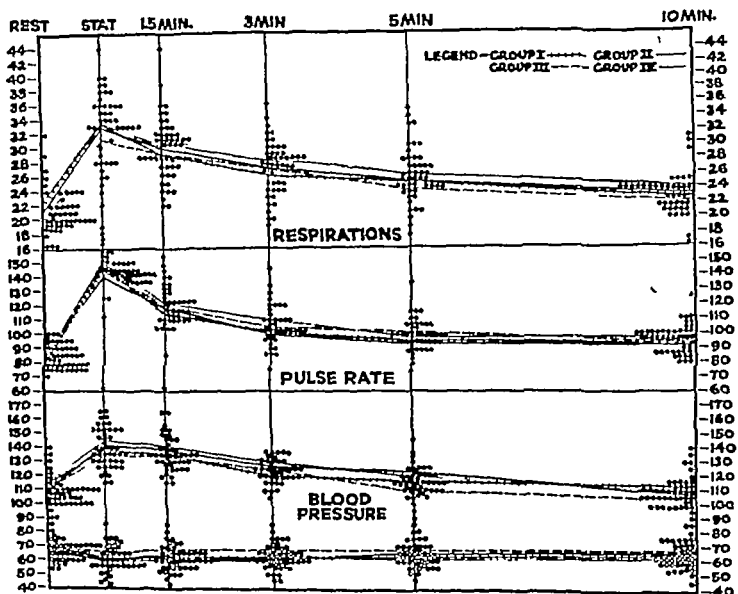


CHART 3 RUNNING IN PLACE

is a broad spread which is just as marked in the controls as in the malarial patients. However, the averages of the groups are remarkably similar. The final average of all of the patients and the final average of all the controls are compared in Chart 5. It is apparent that there is a small but constant elevation of the average pulse and respiratory rates in the malarial patients as compared with the controls. Although this difference is slight, its constancy, considering 150 determinations among the malarial patients and 300 among the controls, seems significant, and indicates a definite manifestation of fatigue in the components measured by this test. Although there is a noticeable difference between the average response of the malaria and control subjects there is no consistent significant difference within these two categories, that can be correlated with length of stay in the tropics and type of adjustment, and general physical condition.

There was no appreciable difference between the blood pressure determinations of the malarial patients and the controls

**Schneider Index** The Schneider Index Test, which was employed at one time in aviation medicine to evaluate fatigue in terms of vasomotor instability in pilots, was used by us to measure that manifestation of fatigue (37) This test measures the cardiovascular response to change in posture and to a minimal standardized effort, and is scored on a point system dependent upon the changes in pulse and blood pressure The maximum score attainable is plus 18 The Schneider Index was recently used by Clinton and Thorn (38) in a study of 21

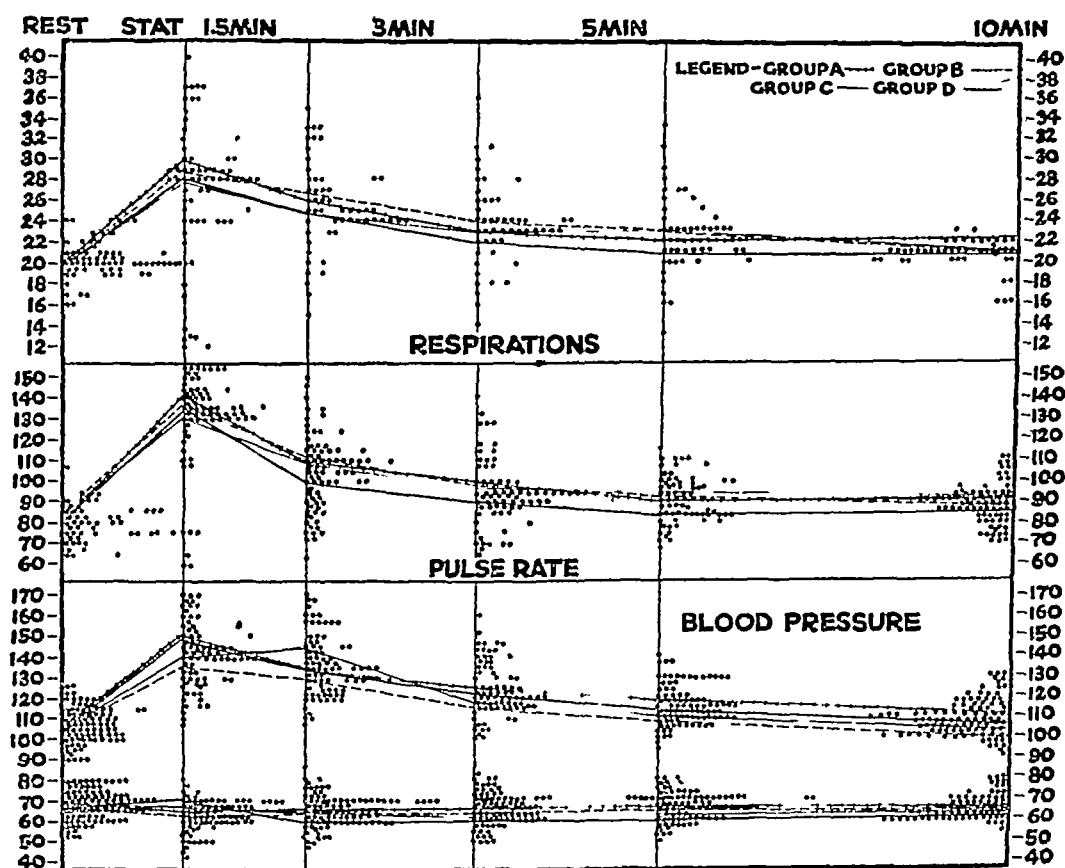


CHART 4 RUNNING IN PLACE—CONTROLS

airline pilots who were found to have indices ranging from 17 to 6 with a mean of 12 The test was done according to the method outlined by Armstrong (39) At least three tests were done on each individual on three successive days In certain instances the results obtained from day to day showed considerable disparity, and in these the test was repeated until comparable figures were obtained The Schneider Index was always determined before any other fatigue tests were attempted The results in the fifty patients and the one hundred controls are shown in Table 20 The malarial patients had an average index of 7.8 while that of the controls was 9.8 The range within these two main categories was wide, and there was considerable overlapping between them Schneider suggested

that a consistent index of 9 or below represented a sufficient degree of fatigue to warrant attention. Among the malarial patients, general physical condition and type of adjustment did not have a significant effect on the Index. Length of stay in the tropics had no demonstrable effect on the index in the control group. Among the controls, those individuals in good physical condition and well adjusted had a slightly higher index 10.5, in contrast to the average index of 7.8 for the malarial patients. The great range of performance did not justify the

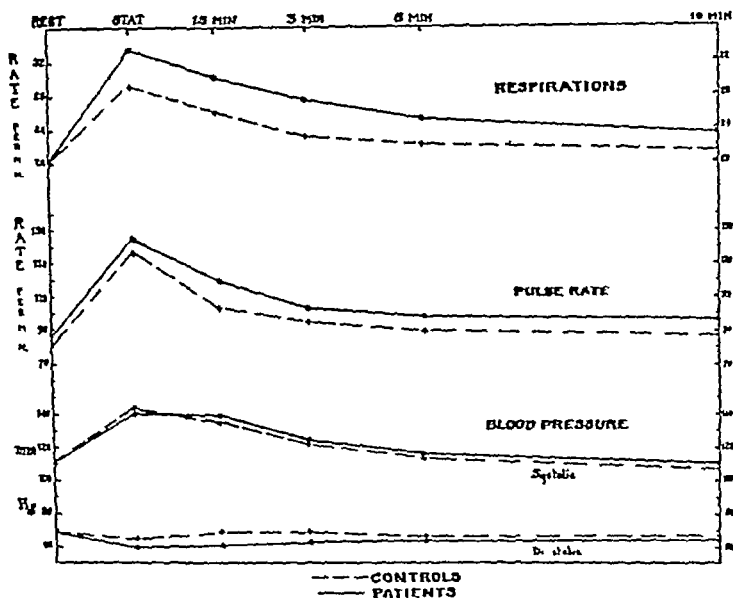


CHART 5 RUNNING IN PLACE TEST

selection of any arbitrary figure below which a significant degree of fatigue could be expected.

**Postural Hypotension** Because of the frequent complaint in chronic malarial patients of dizziness and momentary "blackouts" when assuming the erect posture, each soldier was studied for evidence of postural hypotension by means of the tilt table. A seatless table was so constructed that a subject could be instantaneously swung from the horizontal to the vertical position. The only support was a large ample foot rest. At the end of a five minute resting period pulse and blood pressure were taken, and the table was swung from the horizontal to the vertical, and pulse and blood pressure readings were taken immediately, and at intervals of 1½, 3, 5, and 10 minutes thereafter. Timing was done with a

stop watch Three such tests were done on each malarial and control subject on successive days Again the results were graphed on a standard chart, and the mean of all three tests determined for each individual As in the running in place test, the similarity of pattern in each subject, as well as the degree of response, was found to justify the determination of such a mean These mean values were graphed on master charts (Charts 6 and 7) for both the malarial patients and the controls Here, as in the running in place test, there was a broad scattering of the mean individual responses throughout all the groups, in both the malarial and control subjects, as represented by the black dots However, it can be seen from Chart 6 how very similar both in degree and pattern were the average responses of the four groups of malarial subjects Chart 7 shows the same relationship between the averages of the control groups Finally,

TABLE 20

*Showing the average and range of three or more determinations of the Schneider Index in fifty chronic malarial patients and one hundred controls*

MALARIAL PATIENTS	GROUP ONE (GOOD PHYS, GOOD ADJ)	GROUP TWO (POOR PHYS, GOOD ADJ)	GROUP THREE (POOR PHYS, POOR ADJ)	GROUP FOUR (GOOD PHYS, POOR ADJ)
Number	14	12	13	11
Range	3 to 13	5 to 11	3 to 11	5 to 16
Average	7.3	8	7	9
CONTROLS	GROUP A (GOOD PHYS, GOOD ADJ) TROPICS 22 MOS	GROUP B (GOOD PHYS, GOOD ADJ) TROPICS 2 MOS	GROUP C (GOOD PHYS, POOR ADJ) TROPICS 22 MOS	GROUP D (POOR PHYS, POOR ADJ) TROPICS 22 MOS
Number	38	37	15	10
Range	5 to 18	5 to 17	3 to 13	4 to 13
Average	10.6	10.5	9.4	9
AVERAGE	MALARIAL PATIENTS 7.8		CONTROLS 9.8	

comparison between the average response for all the malarial subjects with that of the average for all of the controls (Chart 8) discloses in the malarial subjects a slight but definite tendency for the systolic blood pressure to fall to a greater degree during the early minutes of the test, and little tendency for the diastolic pressure to rise as an immediate response to tilting

Nineteen, or 38%, of the malarial patients showed varying tendencies toward postural hypotension in this tilt table test, as indicated by signs and symptoms, and these patients were evenly distributed among the four groups First noted symptoms were a tendency to sighing respirations, yawning, restlessness and nausea, followed by excessive sweating and the complaints of dizziness and weakness The average response pattern of these nineteen patients is shown in Chart 8 It can be seen that the tendencies in the response of the malarial patients which distinguished them from the controls, are to a slight degree more exaggerated among these patients with manifestations of postural hypotension.

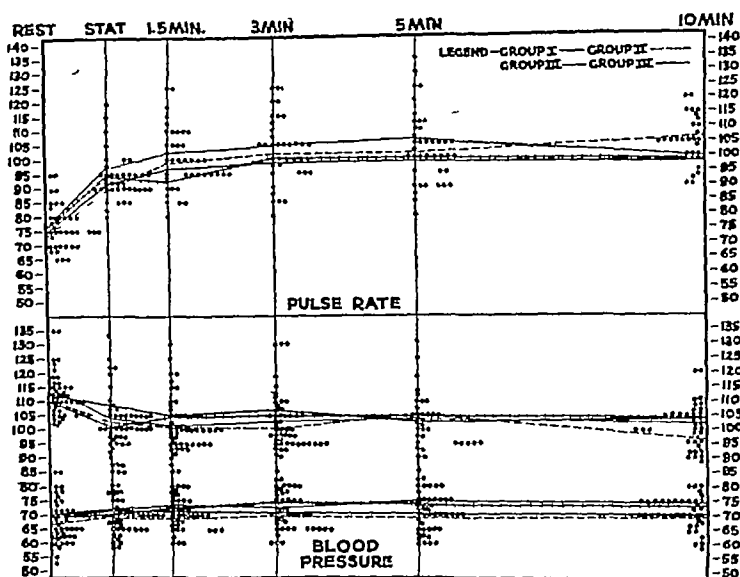


CHART 6 POSTURAL HYPOTENSION STUDIES—PATIENTS

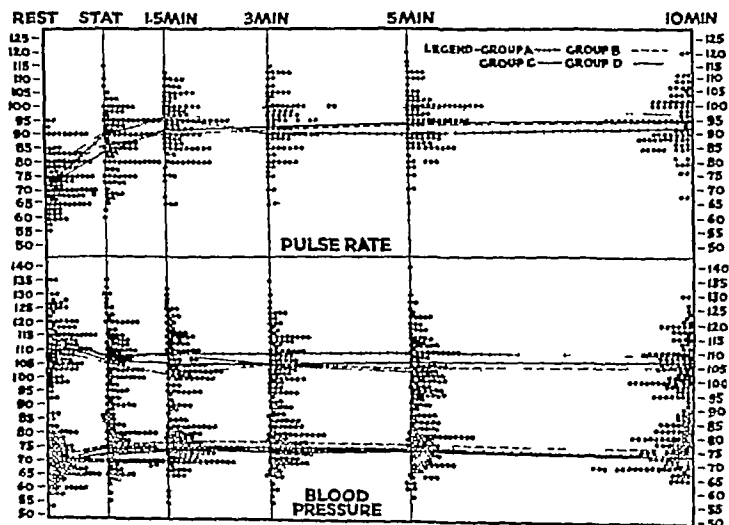


CHART 7 POSTURAL HYPOTENSION STUDIES—CONTROLS



Twenty of the fifty subjects studied gave a history of "blackouts" at some time or other, and 13 of these are included among this group of 19 showing indications of postural hypotension by this test. Twelve of the twenty had complained occasionally of dizziness and "blackouts" prior to the onset of malaria. Among the controls, only 2 of the 100 subjects showed evidences of postural hypotension in this tilt table test.

*Hines Cold Pressor Test* The Cold pressor test described by Hines (36), was performed on the fifty malarial patients and eighty three of the normal controls

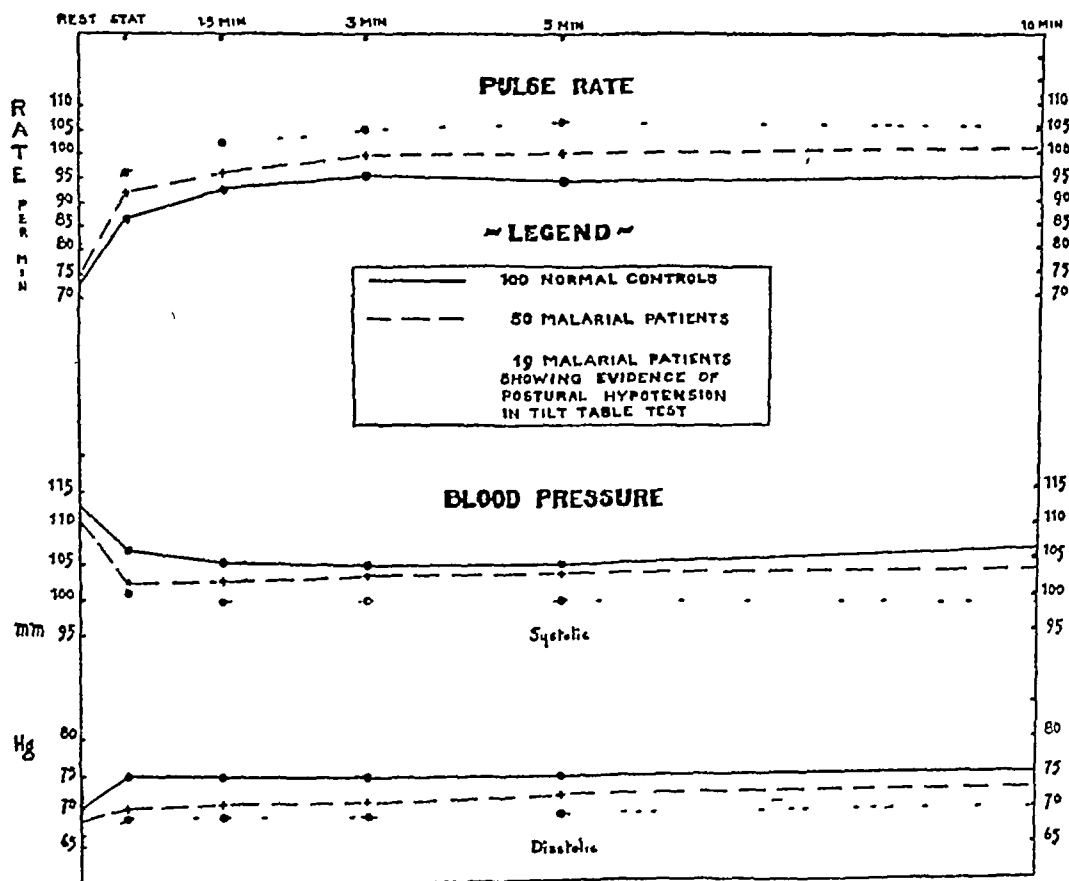


CHART 8 POSTURAL HYPOTENSION STUDIES—COMPARISON OF PATIENTS AND CONTROLS

Table 21 shows the results of the single test. It can be seen that there is a slightly higher percentage of hyper-reactors among the malarial patients as compared with the controls, but it does not appear to be a significant difference.

*Correlation of Data* The general differences between the malarial patients and the controls in the performance of these tests have already been described, and are apparent in the tables and charts. It can be said that the performance in these tests of soldiers with recurrent malaria was, on the whole, not as good as the performance of soldiers who had not had recurrent malaria. Adjustment and length of stay in the tropics did not seem per se to have any appreciable effect on these particular tests, within either the malarial or control groups. The consistent differences noted between the average response of all the malarial patients

compared with the average of all the control subjects must then be related to what differences existed between these two main categories. Recurrent attacks of malaria seemed to be the most striking factor, but in addition, the fact that these individuals had undergone the wear and tear of combat with all its attendant physical and psychological stresses and strains cannot be underestimated, and the relative degree that both chronic malaria and these other factors contributed toward the total result is chiefly a matter of speculation. That no greater difference appeared between those in good physical condition and those in poor physical condition among the two main categories is probably due to the inherent limitations of the fatigue tests themselves.

To show in what features, if any, the responses to the Schneider, Hines, running in place and the postural hypotension tests might be related, further correlation was attempted. This analysis included a detailed comparison of all the

TABLE 21

*Showing the results of a single Hines Cold Pressor test done on 50 malaria patients and 83 controls expressed as hyper and hypo reactors*

MALARIA PATIENTS	GROUP ONE (GOOD PHYS., GOOD ADJ.)	GROUP TWO (POOR PHYS., GOOD ADJ.)	GROUP THREE (POOR PHYS., POOR ADJ.)	GROUP FOUR (GOOD PHYS., POOR ADJ.)	TOTAL
Number	14	12	13	11	
Hyperreactors	8	6	7	8	29 58%
Hyporeactors	6	6	6	3	21 42%
CONTROLS	GROUP A (GOOD PHYS. GOOD ADJ.) TROPICS 22 MOS.	GROUP B (GOOD PHYS. GOOD ADJ.) TROPICS 2 MOS.	GROUP C (GOOD PHYS., POOR ADJ.) TROPICS 22 MOS.	GROUP D (POOR PHYS., POOR ADJ.) TROPICS 22 MOS.	TOTAL
Number	37	32	3	9	
Hyperreactors	16	19	3	1	39 47%
Hyporeactors	21	13	2	8	44 53%

components of these tests. From the analysis it was found that there was no correlation between the reaction in the Hines test and a tendency to excessive systolic elevation of the blood pressure after running in place, nor was there any relationship between the hyper and hyporeactors in the Hines test with the high or low Schneider indices. As one might expect from the nature of the Schneider test, those individuals in all groups who had higher Schneider indices showed less tendency to develop a marked increase in the pulse rate as well as an abnormal fall of the systolic pressure upon immediate tilting. Although the controls as a group showed a greater tendency to an elevation of the diastolic pressure as an immediate response to tilting (Chart 7), there was no relationship between this and a high or low Schneider Index. In comparing the level of the Schneider Index and the degree of elevation of the systolic pressure after running, there was no significant correlation. The rate at which the pulse returned to normal after running was generally directly related to the level of the Schneider Index, except

in Group III of the malarial patients, the group in poor physical condition and poorly adjusted. In this group there was a disparity between the rate at which the pulse returned to normal after running and the level of the Schneider Index, the converse of the tendency noted above in the other groups. There was no apparent explanation for this.

#### THE RORSCHACH TEST

The Rorschach Test is a means of gaining information concerning personality structure which has been found to possess unusual merit. The subject is asked to tell what he sees in each of ten standardized ink-blot. The rationale of the technique lies in the projection of interpretations into a meaningless blot, and it has been demonstrated that the responses are dependent upon personality structure. The performance is analyzed in a number of ways, by portions of the blot utilized, the determinants of responses, the varieties of movement, shading, color, and the accuracy of form, the content according to the general categories of things seen, and whether commonplace or original. The analysis of the personality is made by a correlation of a number of factors. The utilization of the procedure is complicated and requires considerable specialized training.

The test was given to 46 of the 50 malarial subjects to determine whether their neurasthenic condition would be reflected in the test, and whether differences existed between the four groups into which the subjects were divided, according to physical condition and adjustment. As the test was utilized for a comparison of groups, rather than for the study of individual personality structure, it was essential that a completely uniform technique be used with each subject. The directions given the patient were limited to those recommended by Klopfer and Kelly (40), in which emphasis is placed upon the initiative and spontaneity of the subject in reacting to a strange task. No prompting or urging is permitted after the original directions are given.

The results of the 46 tests were very surprising because of the paucity of responses and the qualitatively poor performances as a whole. For the most part, good performances were found only among the more intelligent subjects. The results, when contrasted with standards usually accepted as normal, were so poor that it did not seem likely that the cause could lie in the neurasthenic condition of the patients alone. Two control groups were established. The first group consisted of 50 subjects who had served overseas in the tropics approximately the same length of time as the malarial patients but had never suffered from malaria, the second group consisted of 50 soldiers recently arrived in the tropics, to control the possibility that prolonged sojourn in the tropics influenced the results of the testing. There was no appreciable difference between the results obtained in the two control series, and the groups were combined. As intelligence level was an important factor in the performance of the malarial series, the control groups were selected to approximate closely the distribution of intelligence in the malarial series. Both malarial series and controls approximated the general white population of the army in intellectual resources. The control group was slightly inferior in intelligence ratings, a difference which

would lead to an expectation of slightly poorer performance on the Rorschach. Subjects with an intelligence quotient of over 110 (Binet Mental age of 14 years equivalent to 100, and to Army Classification Rating of 100) were considered superior, those between 90 and 110 as average, and those below 90 as inferior. The general distribution of intelligence levels is shown in Table 22.

The control series also yielded results that were poorer in quantity and quality than anticipated. In a further control study which is not of significance to this paper, it was shown that the reason lay in the rigid technique utilized. The directions permitted by the method outlined by Klopfer and Kelly (40) require too much initiative, particularly for persons with average intelligence or less, at least in an army setting. However, the technique was utilized in both controls and malarial series in this study, the same conditions apply to both series, and there were very striking differences in performance of the malarial patients as contrasted with the controls. It is even possible that the technique which demanded initiative and spontaneity was more conducive to uncovering deficiencies in these spheres, than a technique which permitted fuller instruction and encouragement.

TABLE 22

*Showing the distribution of intelligence in the 46 malarial patients and the 100 controls*

	SUPERIOR	AVERAGE	INFERIOR
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Malarial subjects	32.6	45.6	21.7
Controls	32.0	38.0	30.0

The results of the test were broken down into the various conventional scoring categories and configurations and the results for each of the four groups of malarial subjects, the entire malarial series, and the 100 controls were compared. However, for simplification, only the data which seem particularly pertinent to this study will be presented here. Table 23 presents the means for each of the groups, for the composite malarial series, and for the control series. Table 24 contrasts the results of the malarial and control series as broken down according to intelligence levels. It will be noted that the differences between the malarial and control subjects with superior intelligence are extremely marked.

Both tables show the paucity of responses given by the malarial subjects. It is most marked in the superior group, where 73% gave fewer than 12 responses in contrast to 28% of the controls. This is considered an indication that less effort and energy were expended, for although a large number of responses to the ten cards is not essential to a good performance, persons of superior intelligence are expected to give more than 12 responses. An unusually high proportion of the responses utilized the whole blot ("Whole Response"), rather than portions of the blot. If such responses are due to the synthesis of parts into a well organized whole they indicate good constructive intelligence, but here a very high proportion were simple and rather obvious responses, lacking quality. The high propor-

tion of such "cheap whole responses" such as "bats," "insignia," "maps" etc, indicates that the subjects resorted to simple responses rather than exert themselves to form answers of good quality. This sort of performance is considered indicative of neurasthenic trends when found in persons of high intelligence.

The perception of human movement in the blots is related to the responsiveness to stimuli arising from within the individual, and has been correlated with initiative and utilization of one's resources. Such responses are not expected of persons of low intelligence, but persons of superior intelligence usually give several. Only 7% of the superior malarial subjects gave more than two movement responses whereas 38% of the superior controls gave more than two. Perception of animal movement indicates responsiveness to inner stimuli at a less mature and more instinctual level. There was lower performance at all three intel-

TABLE 23

*Showing an analysis of pertinent data obtained by the Rorschach Test, on 46 patients with chronic recurrent benign tertian malaria, and 100 control subjects*

	GROUP I	GROUP II	GROUP III	GROUP IV	MALARIAL SERIES (46 CASES)	CONTROLS (100 CASES)
Average number of Responses per patient	12.8	12.5	9.9	15.7	12.6	17.7
Percentage of Responses that are "Whole" Responses	59%	59%	65%	63%	61%	45%
Percentage of Responses that are "Cheap" Responses	37%	42%	38%	39%	39%	31%
Average number of Human Movement Responses	0.8	0.9	0.6	0.7	0.8	1.3
Average number of Animal Movement Responses	1.8	1.6	2.4	1.8	1.9	3.4
Sum of Color Responses	1.0	1.2	0.8	1.4	1.1	1.5
Percentage of Total Responses elicited by Cards 8, 9, 10	31%	31%	25%	25%	28%	35%
Mean Time for Responses in Seconds	48	46	75	59	51	52
Average number of Cards rejected per patient	1.3	1.3	2.1	1.5	1.6	1.1

lectual levels. The results suggest that the malarial series was less responsive to inner promptings and showed less initiative than the controls.

Responsiveness to external stimuli shows a similar flattening. Color is scarcely utilized, a defect particularly noticeable in the subjects of superior intelligence. Perhaps more important is that color does not stimulate to responsiveness as noted in the poverty of responses to the last three cards which are highly colored (Percentage of Total Responses elicited by cards 8, 9, 10). The paucity of responsiveness to color may also indicate some degree of emotional flattening.

The time required in finding responses is significantly lengthened only in Group III of the malarial subjects, where it is quite striking. Finally, it is to be noted that more cards were rejected by the malarial patients, the blot having failed to evoke any response. Rejections are uncommon, particularly among intelligent persons, but 33% of the superior malarial subjects rejected more than

2 cards, as contrasted with 9% of the superior controls. The rejections appear as further evidence of the diminished sensitivity or the increased apathy of the malarial subjects.

TABLE 24

*Showing the range of responses in the Rorschach Test, in relation to the distribution of intelligence for the 46 malarial patients and the 100 controls*

	RANGE OF RE SPONSES	46 MALARIAL PATIENTS				100 CONTROL SUBJECTS			
		Superior (32.6%)	Average (45.6%)	Inferior (21.7%)	Total	Superior (32.0%)	Average (38.0%)	Inferior (30.0%)	Total
	Intelligence	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent
Average number of Responses per patient	0 to 12	73	71	50	67	28	61	67	52
	over 12	27	29	50	33	72	39	33	48
Percentage of Responses that are "Whole" Responses	0 to 29%	13	10	30	15	34	25	20	26
	30 to 59%	27	33	30	33	44	47	40	44
	over 60%	60	52	40	52	22	20	40	30
Percentage of Responses that are "Cheap" Responses	0 to 49%	60	67	70	65	94	69	64	75
	over 50%	40	33	30	35	6	31	37	25
Average number of Human Movement Responses	0 to 2	93	95	100	96	62	80	93	81
	over 2	7	5	0	4	38	14	7	19
Average number of Animal Movement Responses	0 to 2	60	76	80	72	47	64	53	52
	over 2	40	24	20	28	53	36	47	48
Sum of Color Responses	0 to 2	80	90	90	88	50	87	88	78
	over 2	20	10	10	12	41	13	12	22
Percentage of Total Responses elicited by Cards 8, 9, 10	0 to 29%	47	48	50	48	16	34	27	26
	30 to 49%	53	52	50	52	62	46	61	57
	over 50%	0	0	0	0	22	21	12	17
Mean Time for Responses in Seconds	over 60	40	44	25	40	30	34	11	23
Average number of Cards rejected per patient	0 to 2	67	72	70	70	91	71	87	82
	over 2	33	28	30	30	9	29	13	18

Elaborate interpretations of the findings are avoided, and attention is drawn to the obvious and clear-cut indications. The picture obtained is one of diminished output of energy, and lessened sensitivity to stimuli, both from within the individual and from his surroundings. The subjects tend to be more apathetic and disinterested than the controls. The impression is gained that the inertia goes beyond the volitional, and has cut deeply into the behavioral pattern.

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lectual levels. The results suggest that the malarial series was less responsive to inner promptings and showed less initiative than the controls.

Responsiveness to external stimuli shows a similar flattening. Color is scarcely utilized, a defect particularly noticeable in the subjects of superior intelligence. Perhaps more important is that color does not stimulate to responsiveness as noted in the poverty of responses to the last three cards which are highly colored (Percentage of Total Responses elicited by cards 8, 9, 10). The paucity of responsiveness to color may also indicate some degree of emotional flattening.

The time required in finding responses is significantly lengthened only in Group III of the malarial subjects, where it is quite striking. Finally, it is to be noted that more cards were rejected by the malarial patients, the blot having failed to evoke any response. Rejections are uncommon, particularly among intelligent persons, but 33% of the superior malarial subjects rejected more than

2 cards, as contrasted with 9% of the superior controls. The rejections appear as further evidence of the diminished sensitivity or the increased apathy of the malarial subjects.

TABLE 24

*Showing the range of responses in the Rorschach Test, in relation to the distribution of intelligence for the 46 malarial patients and the 100 controls*

	RANGE OF RE- SPONSES	46 MALARIAL PATIENTS				100 CONTROL SUBJECTS			
	Intelligence	Superior (32.6%)	Average (45.6%)	Inferior (21.7%)	Total	Superior (32.0%)	Average (38.0%)	Inferior (30.0%)	Total
		per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent
Average number of Re- sponses per patient	0 to 12	73	71	50	67	28	61	67	52
	over 12	27	29	50	33	72	39	33	48
Percentage of Responses that are "Whole" Re- sponses	0 to 29%	13	10	30	15	34	25	20	26
	30 to 59%	27	38	30	33	44	47	40	44
	over 60%	60	52	40	52	22	29	40	30
Percentage of Responses that are "Cheap" Re- sponses	0 to 49%	60	67	70	65	64	69	64	75
	over 50%	40	33	30	35	6	31	37	25
Average number of Human Movement Responses	0 to 2	93	95	100	96	62	86	93	81
	over 2	7	5	0	4	38	14	7	19
Average number of Animal Movement Responses	0 to 2	60	76	80	72	47	64	53	52
	over 2	40	24	20	28	53	36	47	48
Sum of Color Responses	0 to 2	80	90	90	88	59	87	88	78
	over 2	20	10	10	12	41	13	12	22
Percentage of Total Re- sponses elicited by Cards 8, 9, 10	0 to 29%	47	48	50	48	16	34	27	26
	30 to 49%	53	52	50	52	62	45	61	57
	over 50%	0	0	0	0	22	21	12	17
Mean Time for Responses in Seconds	over 60	40	44	25	40	30	34	11	23
Average number of Cards rejected per patient	0 to 2	67	72	70	70	91	71	87	82
	over 2	33	28	30	30	9	29	13	18

Elaborate interpretations of the findings are avoided, and attention is drawn to the obvious and clear-cut indications. The picture obtained is one of diminished output of energy, and lessened sensitivity to stimuli, both from within the individual and from his surroundings. The subjects tend to be more apathetic and disinterested than the controls. The impression is gained that the inertia goes beyond the volitional, and has cut deeply into the behavioral pattern.



Group III of the malarial series requires special attention. It was this group of subjects, in poor physical condition and poorly adjusted, that had more complaints than the other groups, and was more obviously neurasthenic. Table 23 shows the unusually poor performance of this group on the Rorschach Test, with the total number of responses, human movement responses, and color responses, approximately but half as numerous as in the controls, and with almost twice as many rejections of cards. The poor performance of this group is the more significant, as it contains more subjects of superior intelligence than the other groups and but one subject of inferior intelligence. The low means for the scores are not due to extremely poor performance on the part of a few individuals. Nine of the twelve subjects or 75% of Group III showed very poor performance, as contrasted to 42% of the malarial series as a whole, and to 21% of the control series.

Group IV, the other poorly adjusted group, which was, in contrast, in good physical condition, exhibited a better performance than Group III, and was similar to those in Groups I and II. This would suggest that the technique measured a true apathy and fatigue rather than simple disinterest.

The Rorschach Test corroborated the clinical impression that the malarial subjects had less vitality, initiative, and interest than the average soldier. Further, the correlation of the test results with the clinical impression of the poor condition of the subjects in Group III is striking. Whether as a result of the recurrent malaria or as a result of their poor adjustment to the circumstances, or both, their psychic energy had been markedly diminished. This in turn was reflected in their total behavioral pattern. The projective technique of the Rorschach Test displayed objectively that which was observed clinically. It is suggested that the emotional and mental state of the patient reflects the total state of the individual with greater sensitivity, and that this state was measured by the Rorschach technique.

#### PSYCHOSOMATIC STUDY

In the study of the effects of malaria upon the patients, and in the attempts to understand their symptomatology, the reaction of the personality to the illness was seen to be of considerable importance. The malaria influenced the adjustment of the soldier, and maladjustments, at times, eventually altered his physical condition. Then, too, the malaria was but one of several factors producing neurasthenic symptoms. Malaria, situational factors, and personality traits were intimately interwoven, and could not be differentiated as single etiologic influences. The neglect of one would lead to an overestimation of the others as a cause of symptoms. The effect of the recurrent malaria is to be understood as one factor in the total situation in which a variety of influences might lead to neurasthenic complaints. The general condition of the troops did not permit symptoms to be ascribed to malaria uncritically. The rôle of emotional influences was far greater than would be anticipated in civilian practice, or even in military medicine in the United States. The troops had been subjected to a prolonged period of unusual stresses from which they were recuperating on this island, as well as from malaria. Psychoneurosis and malaria were the predomi-

nant causes of hospitalization The two conditions were often affecting the same soldiers, and the selection of the one or the other as a primary diagnosis was not infrequently a moot question The person and the illness is viewed against the background The soldier is an integral part of his unit and reacts to the prevailing sentiments of the unit, particularly when separated from the remainder of society in an isolated post on a tropical island The influences at work upon this group of patients may not be reduplicated elsewhere, but it is necessary to understand them, before it can be understood why personality problems, seemingly extraneous to the problem of malaria, intrude themselves upon the study so forcibly It is not possible nor desirable to review the extremely complicated topic of army morale, but simply to afford an understanding of the background of the men studied

The units from which practically all of the 50 patients came had been called up with the National Guard more than a year prior to the outbreak of the war Almost immediately after the onset of hostilities, and before the nation had shown any indications of total mobilization, they had been sent to a forward outpost They had lived there under primitive conditions, and without benefit of the recreational facilities which later lightened the monotony of island life Many were stationed at isolated posts in the jungle, guarding the coast against attack which was believed imminent Some failed to make the necessary adjustment and were removed from the units After seven or eight months they were thrust, into one of the most gruelling and harrowing struggles ever fought by American soldiers The tactics of the Jap were strange and brought many surprises to these first troops engaged Supplies were meager, and living conditions relatively poor, even in comparison with later campaigns in the area The men fought bravely when the campaign seemed almost hopeless, but often with intense fear When they left Guadalcanal after four or five months the island was secure They looked forward to a period of rest, recuperation, and a chance to enjoy themselves Already there were rumors of return to the United States because of the poor condition of the troops Almost all the men had suffered one or more attacks of malaria, and they were to be cured

At first, any place was better than Guadalcanal The island selected for recuperation was free from malaria and aerial attack, but it was also deficient in white girls and recreational facilities The soldier was in a small, isolated encampment, where he remained for ten months while efforts were made to rehabilitate the units for combat Hopes rose and fell with rumor Often the men believed they were about to return to combat, and almost as often believed that they might be sent home for rest The optimal time for recuperation passed but the soldiers were not in condition Months of intense boredom continued, permitting time for reflection Combat on Guadalcanal had not whetted appetites for further jungle fighting It had been terror, and not glory Men were willing but not enthusiastic, and they hoped that further fighting on the Solomons would be unnecessary for them Boredom, relieved mainly by familiar manoeuvres, gave rise to nostalgia Unhappy in reality, daydreaming of a more pleasant past became a common preoccupation The future held little



about 45 minutes. The purpose was to gain an opinion of the subject's adjustment to the current situation, including the malaria, and to obtain a picture of their background, both in personality and situational factors. It was not anticipated that these soldiers who were not seeking psychiatric help would reveal themselves fully in a single interview. Emphasis was placed upon having the subject tell how he felt, and in expressing his attitudes. In rather informal fashion queries were inserted concerning the family background, previous stability, behavior in civilian life, reactions to combat, concern over malaria, the depth of his nostalgia, and attitudes towards his unit. Subjects were given the opportunity to express their dissatisfactions and resentments without fear of condemnation. They understood the purpose of the interview and were anxious, to a surprising degree, to offer their opinions about various situations, and to tell how they had reacted to various incidents. The psychiatrist's familiarity with the men and officers in these units, the opinions held, the detailed history of the units and of the morale in the units etc., aided in the attainment of rapport and in covering considerable ground in a brief space of time. Furthermore, the amplified medical history, which inquired in detail into family background, personal civilian history, adjustments to situational factors in Army life, and symptomatology, was available. Analysis of this material was enhanced by the impressions gained of each individual during a week's observation.

The psychiatric interview was amplified by intelligence tests and the Rorschach Test. Stanford-Binet and Kohs' block intelligence tests were given, as it had been thought likely that men of lower intelligence would have more difficulty in making the adjustments to illness and the isolated life. It had been noted prior to the study that the definitely feeble-minded were unsuited for jungle combat. The distribution of intelligence in the 50 subjects paralleled closely that of the white population of the army in general. There was no apparent relationship between adjustment and intelligence. In the four groups there was no significant difference between the mean intelligence levels. The Rorschach Test was utilized in a limited fashion, and has been discussed among the studies of fatigue.

Before surveying the relationship of the symptoms to adjustment, and before discussing the underlying personality traits that affected adjustment, the situational factors that confronted the subjects will be reviewed briefly. Some were scarcely troubled by any of them, while others were badly affected. The topics to be discussed influenced a large proportion of the patients.

*Repeated hospitalizations.* Each of the numerous hospitalizations removed the soldier from duty, and brought him into intimate contact with men who were to be returned to the United States. The inactivity in the hospitals permitted time for reflections in an atmosphere where conversation and interests tended to center about home. The morale of the patients in hospitals, despite effort to bolster it, was quite definitely lower than that of men outside of hospitals, particularly as there tended to be a piling up of psychiatric casualties in the hospitals. The hope of being dispositioned to the United States was more or less consciously and honestly present. They could not but hope that they would be deemed sufficiently worn to be sent home. Many men admitted that homesickness was only

a serious problem when idle in the hospitals, and sought rapid discharge. The separation from the unit, sometimes prolonged to permit full recuperation, permitted the men to lose their sense of being a member of a unit, and the willingness and even desire to share the trials of war with their friends.

*Inability to remain at full duty* Even when discharged from the hospitals, many of these soldiers not able to tolerate full duty were forced into relative inactivity because of weakness, or to avoid provocation of malarial attacks by strenuous activity. It is one thing for men to remain away from home when serving a purpose they realize is useful, but it is quite different when they feel that they are wasting their time and are more hindrance than help to their units. Further, the inability to perform full duty well led to an impasse which limited their army careers. Others could transfer to the air-corps, attend officer's candidate school, volunteer to join commando units etc, *but no one seemed interested in giving special training to the malarious*. Finally, it became impossible to receive higher ratings, and feeling that rewards for good and lengthy service were denied them when new arrivals were promoted over their heads, they tended to lose interest and became resentful.

*A source of resentment* As has been indicated, there were numerous causes for resentment without the additional contribution of malaria. Some men suffering repeated attacks of malaria felt that they had been unfortunate, or had been discriminated against because they had not been sent home, while friends who appeared no sicker had been dispositioned. Why must they carry on, ill as they were, when there were still many men who had never been overseas, and men to whom the war was so distant that they could strike in defense factories? They had fought the crucial battle and were ill. Resentments have a way of spreading from topic to topic, embittering and causing physical distress.

*Concern over illness* A most important influence upon adjustment was the soldier's concern over the malarial illness itself, and its effects upon his future well-being and happiness. *Malaria had become so commonplace in the area that some medical officers seemed to forget that the patient might not take it lightly*. The reassurances given to the patient early in the course of his illness had proven erroneous, and the patient was apt to give little heed to reassurance given casually. Thirty-three of the 50 patients studied, or 66%, had fears and misapprehensions that weighed upon them, and were largely unnecessary. Twenty-one of the 24 poorly adjusted subjects, or 88%, had such concerns, and in some they were serious preoccupations. None of the patients studied had any really thorough understanding of what malaria was, and what it could do to them in the future. Only 19 of the 50 had any insight as to what might be expected of the disease in the immediate or more distant future. Of the 33 patients with concerns over malaria, 23 had no insight whatsoever. The inadequacy of the insight and understanding is emphasized by the fact that even among the 19 patients with some degree of insight, 10 still had unnecessary concerns. There was no correlation between level of intelligence and the degree of understanding of the illness.

The patients had gradually realized that present medical therapy was insufficient to cure their malaria, and some of them believed that because the malaria

had not subsided as prognosticated, the infection from which they suffered differed from other forms, and would never cease recurring. The fear of some degree of permanent disability was extremely prevalent, occurring in approximately all of the 66% who were worried about the malaria. They feared, or firmly believed, that they would be unable to obtain decent jobs, as their recurrent illness would be held against them by employers, as it seemed to them it was in the army. They worried about supporting wives and children, and some of the men who were engaged to marry seriously contemplated breaking their engagements. Some envisioned years during which they would be unable to work steadily and would live on pensions, or in Veteran's hospitals. Some believed that the recurrent attacks had already, or would eventually, leave their health permanently impaired, even though the malaria eventually subsided. It was for this reason that the subjects of the study participated gladly, to learn if they had already suffered some permanent damage from the malaria or the atabrine. The concerns were often deep, and men became markedly depressed when contemplating a barren and hopeless future. Occasionally, astonishing changes in spirits occurred, accompanied by considerable diminution of complaints, after the patients were carefully reassured that attacks would taper off, and occur rarely after two or three years (41-43).

Only a few patients were still apprehensive over further single attacks as they had learned that serious complications were extremely rare. However, they had worried earlier in the course of the illness for they had seen or heard of deaths from cerebral malaria and blackwater fever. In a few, some lingering apprehension over taking atabrine remained, but at one period such concerns had been fairly prominent. Beliefs had existed that atabrine caused sterility or impotence or other bodily impairments. These concerns had been carefully combatted in the area to improve atabrine discipline. One patient had suffered from persistent vomiting while taking atabrine prophylactically, and one had suffered from a mild confusional state when receiving large dosage of atabrine, but both received quinine prophylactically and therapeutically, and their intolerance was not a problem.

While still in combat units, many of the 50 patients worried that they would be unable to survive combat because of their debility. They recalled that their lives had depended upon endurance, at times, on Guadalcanal, and they no longer had endurance. They feared a malarial attack while exposed and unable to move from their foxholes at night. Removal from combat units brought relief from these warranted fears.

There are other influences of chronic illness that are difficult to evaluate. A sick man, particularly an immature person, is far more likely to feel strong desires to be with his family than a healthy person. Perhaps many wish to be pampered when ill, and there is a tendency to regress to immature ways of behaving and thinking. The psychiatrist learns rapidly not to form judgments of a soldier's capacity for further duty during a malarial attack.

Aside from the concerns over malaria which are common to many soldiers, there were a few individuals in the series with special reasons to be concerned. A soldier who had lost both parents from tuberculosis and had been suspected of

having tuberculosis in childhood, worried when his weight dropped and he was unable to keep himself in good physical condition. A less intelligent individual worried just as much, even though irrationally, that the recurrent attacks might predispose him to cancer, from which both of his parents had died.

A most important consequence, which has been indicated, is that the recurrent malaria provided the soldier who was tired of life in the combat area, and reluctant to return to combat, with an adequate reason to believe that he should be returned to the United States. The illness constantly fosters hopes which are as constantly squelched. He builds up the belief that malaria is benefited by a temperate climate, and that the heat fosters attacks. He has a sensible basis for belief that he should not be returned to combat which permits rationalization of natural fears of further combat. It is very understandable that when others who are in good health are having difficulty in maintaining satisfactory morale, malaria can tip the balance.

The adjustment of the individual depended upon a multiplicity of aggravating forces, and the assets of the personality which enabled them to be handled. Certain situational factors other than the malaria appeared to be equally important in many of these patients, and were productive of the same pattern of symptomatology.

*Nostalgia* was clearly among the most important deterrents to healthy-minded adjustments. The term covered a host of lacks and discontents, and was a feature, either primarily or secondarily, of most illness in the area. It was not the acute nostalgia of the immature youth separated from home for the first time, but a chronic longing for a former existence that contained meaning, enjoyment, and satisfactions, to replace a life filled with futility, frustration, and loneliness. The longing for home was as much a drive away from a life of monotony as a desire for family, girls and friends. Nostalgia was accepted as normal, and all of the patients were anxious to return home as soon as possible. In some the thoughts of home became a constant preoccupation that never left, and led to depressive reactions, in others, to a dissipation of desire and enthusiasm. The men lacked a positive orientation to their current existence. Seventy-eight per cent of the men in the study were homesick to an appreciable extent. In 22% it had become a serious difficulty to the extent that further stay overseas seemed beyond endurance and actually seemed inadvisable in most, because of their depressive state. There were often real concerns, illness or death of parents, infidelity of fiancées etc., but the real situations were present as frequently in those who were but moderately homesick as in those who were severely upset.

*Fed-up* Related to the homesickness, but somewhat different, was the state of mind in which further life in the theater seemed unbearable. The men might not be anxious to get home as much as to obtain a change from the monotony. They had seen friends "crack" and had heard of a few suicides, and worried that eventually they might lose control of themselves, as they were aware of tensions and spells of despondency they had not known at home. The state of being so extremely "fed-up," to the stage where an escape seems urgent, is not apt to be seen in civilian practice from relatively simple situational factors, for prolonged

and severe monotony is usually avoidable. The condition also is not apt to appear in an active combat area, where life, even though distasteful, has a more apparent purpose. In 64% of the subjects, the condition was worthy of note as a factor in adjustment, and in 18% the conditions had become severe.

*Resentment* Resentments over factors other than malaria were multiple, and in some individuals intense, and sufficient to produce adverse influences upon health as well as somatic complaints. *Soldiers resented the "deal" they had received in being brought to an island devoid of recreational facilities and while women, to recuperate, after having already served over a year in isolated positions. Most deeply they resented the idea that they would remain overseas indefinitely, while friends remained at home.* The lack of opportunity for advancement, despite the fact that they were among the first overseas, new officers without combat experience, infantry life, and many other such items, caused bitterness. Some men paid little attention to the gripes that were readily found, whereas others, because of their personality structure, were incapacitated by them. It was estimated that 42% of the subjects were cut deeply by resentments of one type or another, and that approximately 16% were filled with bitterness. The fact that they had not been returned home because of malaria was an additional source of arousal, particularly in the men who were prone to be resentful.

*Climate* Although the tropical climate is usually well borne by those who avoid monotony, and although the so-called "tropical neurasthenia" does not appear to be a climatic matter alone, few who have lived through tropical summers will deny that heat aids enervation. It can reach proportions that make the unwary consider their inertia a sign of ill health from malaria. The prolonged rains which last for weeks or months also limit activity and are conducive to irritability. This study was carried on during mid summer, when mild neurasthenic complaints are common.

*Combat Experience* Only three of the group had suffered from combat neuroses, and they were relatively mild. However, 20% of the group had been badly upset by combat, and worried considerably about how they would fare, if returned to combat. Although a number of the group would have preferred return to combat to the constant indecision concerning the future, none were eager for further fighting in the jungle. The wait had been too long, and there had been too much time to contemplate their past experiences. The constant cross current of rumors as to the future disposition of the units had made for tenseness and irritability.

*Sexual* It is difficult to assess the rôle of sexual problems. Deprivation of opportunity was a source of restlessness and discontent. The fact that all had suffered the same absence of feminine companionship seems to have made the problem less of a source of conflict than in civilian life. Contacts with native women who were available, often increased rather than decreased the conflict. Most men had learned to adjust somehow, and the problem was no longer acute.

There were two general features that aided the adjustment of the men studied. Transfer to non-combat duty, which usually meant to less strenuous activity than line duty, helped all except 10 of the 50 subjects, all but one of whom were



among the poorly adjusted. It appeared as if some individuals had remained in good condition and well adjusted because they had been transferred from the infantry to sedentary duties early in the course of the malaria. In others striking alterations in behavior, complaints and general well-being were found soon after transfer out of the infantry, in which they had been unhappy, and where they had been unable to stand the pace. This was particularly noticeable in several men who had been dreading return to the fighting because of previous severe anxiety in combat. The announcement of the policy of rotation, at about the time this study was started, had a very beneficial effect, particularly as these soldiers had been among the first in the area and could anticipate returning home fairly soon. It gave something tangible to anticipate. The most serious source of resentment and hopelessness was removed. Men who had felt that they could not stay overseas for another month settled down to wait. For the first time in a year, the psychiatrists heard requests not to be sent home on medical disposition. The policy was greeted with scepticism at first, as the men had been disappointed so often that they feared to permit hope to be aroused again. They preferred apathy to another disappointment. Seven of the poorly adjusted men in the study were not benefited by the hope of rotation, because they refused to believe that it would be put into effect. This was considered an ominous sign, for it occurred only among the most disgruntled, or those who were noticeably depressed.

*Adaptability* The manner in which the soldiers adjusted to the circumstances which were present for all, or affected them as individuals in some particular way, differed from person to person depending upon uniqueness of circumstances, but even more upon the integration of the personality. Whether termed adaptability, maturity, stability, or degree of successful integration of the total personality, and whether such factors are believed to be basically constitutional or environmental in origin, the personality which meets the circumstances is at least as important to the end result as the various situational factors. It is to be stressed that this study deals with average individuals. With the exception of three or four individuals in the group, these men had not been separated from their infantry units because of unsuitable adjustment. They had been removed primarily because the frequency of malarial recurrences made them unsuited for combat duty. Actually, it is to be supposed that they were among the more stable in the units, as they were among the last to be separated. It cannot be considered proper to speak glibly of inadaptability in men who had served more than two years overseas, and had survived many months of jungle combat. The soldiers who had suffered from severe combat neuroses or had developed marked psychoneurotic tendencies, and, for the most part, those who had reacted extremely poorly to malaria, had been largely weeded out during the months prior to this study. On the other hand, the increasing duration of the stay overseas, the continuation of the malarial attacks, and the many other influences at work continued, by increasing situational factors, to produce neurotic reactions in the more stable. It was a constant peeling off, which started with the least adaptable, and left a smaller and smaller useful nucleus. No matter how

much we emphasize the rôle of faulty adjustment as a cause of symptomatology in this group, it is certain that, for the most part, they differed markedly from the clear-cut neurotic reactions seen earlier in the year

In individuals, it is possible to form a fairly good estimation of the manner in which situations, intelligence, early training, emotional patterns etc., interact to form the picture seen at the moment. Summing up for a group study presents difficulties. It has been attempted in two ways. The reactivity in the past is examined for indications of instability in childhood and adult life, some fairly definite indications of previous instability are found in 40% of the subjects, when behavior under combat is included, and in 30% prior to combat (see Table 28). Such findings do not, however, indicate any marked instability, except in 3 or 4 cases. The matter will be discussed further in connection with the study of symptomatology. Adaptability was also estimated from the mode of reactivity to current situations, such as the strength of the need to be with parents, difficulties in adjustment to the army, reacting to distressing circumstances by alcoholism, difficulties in making friends, failure to fit into units well, etc. Such estimates for groups are, of course, rough approximations in which the subject's attitude plays a large rôle. They depend largely upon the psychiatrist's experience in evaluating the capacity of soldiers to be of service in the army. Generalizations do not always apply. An occasional alcoholic makes an excellent soldier, a few men who were definitely neurotic were better able to cope with difficulties than the average soldier, because of long experience in handling anxieties or hypochondriacal concerns, men who were worthless in combat settled down and adjusted extremely well in non combat duties. Still, in discussing the groups of patients, it will be seen that there is considerable correlation between personality traits as reflected by past performance, the degree to which the individual is upset by nostalgia, malarial concern, resentments etc., and the symptomatology.

#### ANALYSIS OF GROUPS

The 50 subjects were divided into those who were well adjusted and those who were poorly adjusted to the current situation. Practical criteria of attitudes and performance were utilized. That the division into 26 well adjusted and 24 poorly adjusted was not purely arbitrary, was shown by the fact that the psychiatrist who made a division into these groups independently of the other writers arrived at the same classification, except in the case of three patients. However, there were marked differences within this gross division into two categories. The extremes were readily placed, whereas in the mid-ground there was relatively little difference between the well and poorly adjusted individuals. The distribution was not uniform between those in good physical condition and those in poor physical condition. Group I, consisting of those who were in good physical condition and well adjusted, tended to be better adjusted than those in Group II, who were in poor physical condition. The patients in Group IV comprised those in good physical condition, but who were poorly adjusted, and were definitely more poorly adjusted on the average than the subjects in Group III, who

were in poor physical condition and poorly adjusted. The subjects' adjustments ranged from those in which recurrent attacks of malaria had scarcely impaired the efficiency of the soldier, particularly when removed from strenuous activity, to adaptations which were so poor that it could be stated that the soldier would have been useless for further overseas duty, even if he were not suffering from malaria. There were ten patients at each extreme, and the contrasts between the extremes was striking.

The best adjusted and probably the least worn from malaria, for the two cannot be differentiated completely, had relatively few complaints aside from weakness and fatigability after exercise. They did not complain of lassitude and apathy. They ate and slept well, and few suffered from headaches except with attacks. They complained that it had been difficult to maintain the pace of the infantry, but they had tried to keep up with the others and had rarely fallen out of hikes and manoeuvres despite their fatigue. They had been satisfied in the infantry, had been proud of their units, and had formed close friendships. Transfer to non-combat duty produced no striking change in their conditions, but they found it easier to get along and do satisfactory work. They were not overly concerned about malaria, and though perhaps worried that it might impair their efficiency for a number of years, they did not believe it would influence their future happiness. Homesickness, though present, was not an abiding preoccupation, and they believed that they could wait six months or longer for rotation. There was extremely little resentment. Neurotic and psychopathic traits prior to induction were slight, one soldier had been moderately alcoholic prior to induction and another stammered. They had had their share of difficulties at home which they had been overseas, but had accepted them and not been weighed down by them.

At the other extreme were the men who seemed of little value to the army for reasons other than malaria. They were characterized by feelings of hopelessness. They had given up, and were no longer trying to rehabilitate themselves for overseas duty. They had no faith in anything, and were apathetic and bitter. They complained that they had had nothing but bad breaks, that the army would use them as long as they could walk, that rotation was an empty political gesture, and that they would never be sent home before the war was over. They were preoccupied about home, and worried excessively about their families. They were convinced that the malaria would incapacitate them more or less permanently, and had lost hope in the future. They had not been well adjusted in their outfits, but had not been improved by transfer, as getting home had become their major concern. About half of these men had been poorly adjusted in civilian life. They were thoroughly "fed-up" with life in the area. They complained not only of fatigue after exertion, but that they felt washed-out and tired all of the time. They had become irritable, slept poorly, complained that they ate poorly, and suffered from dizziness, palpitation and shortness of breath. The remaining 30 subjects fell between the extremes, but even among the better adjusted of this 60% of the total group, it was deemed that factors relating to adjustment played a significant role in the production of symptoms. Eleven or approximately 22% were managing well, perhaps after transfer out of combat units, though not

without some degree of difficulty or conflict. Ten patients were in the mid-round, the malaria seemed to have been very difficult for them to handle, but other situational influences were quite prominent. Five of these were placed among the well adjusted and 5 among the poorly adjusted, and the criteria upon which their placement depended could not be stated definitely, and rested in part upon the impression gained during interviews and the week of observation. Nine subjects were having considerable difficulty but remained capable of remaining at unimpaired duty. In contrast to the most poorly adjusted they had not given up, retained pride in themselves, and were combatting their desires to get home as soon as possible. In some respects, it seemed as if these men might be having a more difficult struggle than those who were still more poorly adjusted. The criteria for the groupings will not be described as the difficulties and types of adjustment were varied, but can be pictured from the descriptions of the two extremes. The distribution of the patients in the four groups according to adjustment and physical status used throughout the study can be seen in Table 25. Table 25 indicates that Group I contains better adjusted individuals than

TABLE 25

*Showing relationship of the quality of adjustment to the grouping of the 60 malarial patients*

QUALITY OF ADJUSTMENT	NUMBER IN GROUP I (GOOD PHYSICAL, GOOD ADJUSTMENT)	NUMBER IN GROUP II (POOR PHYSICAL, GOOD ADJUSTMENT)	NUMBER IN GROUP III (POOR PHYSICAL, POOR ADJUSTMENT)	NUMBER IN GROUP IV (GOOD PHYSICAL, POOR ADJUSTMENT)
Good	8	2	—	—
Average	4	7	—	—
Fair	2	3	4	1
Poor	—	—	5	4
Bad	—	—	4	6

Group II, as well as patients who are in better physical condition. It is also apparent that Group III is composed of subjects who, even though in worse physical condition, are somewhat better adjusted than those in Group IV. It is to be recalled that there is little if any difference in physical condition between the subjects in Group I and Group IV, and between those in Group II and Group III, and that the number and frequency of malarial attacks is approximately the same for all groups.

There is a difference between the type of faulty adjustment shown by the Group III and Group IV patients, illustrated by Table 26 which summarizes the history of past stability of the patients. Group IV differs from the other groups, in that it contains a greater proportion of patients who showed psychopathic traits, particularly alcoholism, or neurotic traits, or who had been badly upset by combat. Eighty-two per cent of the subjects in Group IV had shown some evidence of difficulties in adjustment prior to the onset of malaria. In contrast, the soldiers in Group III did not show more evidence of past instability than the better adjusted soldiers. In general, the backgrounds of patients in Group IV resembled more closely those of neurotic patients, and seems pertinent to the

problem of why these men had difficulty in adjusting, even though they had remained in fairly good physical condition. The poor adjustment of those in Group III seemed to be dependent, to a greater degree, on the difficulties ensuing upon their poor physical condition.

It is noted, also, that 38% of all of the subjects who were poorly adjusted had at least one parent who tended to be emotionally unstable, whereas but 19% of the well adjusted had a parent who tended to be unstable. No group correlations could be found with education, intelligence, work or recreational records, or faulty habits of eating or sleeping.

*Current Adjustment* Chart 9 shows an approximation of the relationship between the four groups in their difficulties of adjustment to current circumstances. Although based upon subjective criteria, it is believed that the chart shows the general relationship of the groups in their concerns over malaria, nostalgia,

TABLE 26

*Showing relationship of emotional background to the groups in the 50 malarial patients*

	GROUP I (GOOD PHYS ) (GOOD ADJ )		GROUP II (POOR PHYS ) (GOOD ADJ )		GROUP III (POOR PHYS ) (POOR ADJ )		GROUP IV (GOOD PHYS ) (POOR ADJ )	
	Number	%	Number	%	Number	%	Number	%
Unstable parent	2	14.2	3	24.9	4	30.8	5	45.5
Neurotic traits in childhood	2	14.2	1	8.3	0	0.0	4	36.4
Neurotic traits in adult life	1	7.1	0	0.0	2	15.4	5	45.5
Psychopathic traits incl alcoholism	1	7.1	1	8.3	1	7.7	5	45.5
Badly upset in combat	0	0.0	3	24.9	2	15.4	5	45.5
Individuals with prev neurotic or psychop traits	3	21.3	4	33.2	4	30.8	9	81.9

being "fed-up" with the life, their resentments, and the difficulties in adapting themselves to the situation. It was constructed by estimating the difficulties encountered by each patient, adding them and correcting for the size of the group. It is seen that Groups I and II (well adjusted) are far less concerned about malaria than Groups III and IV (poorly adjusted), that while all were considerably homesick, the difficulties were more marked, and approximately equally severe in Groups III and IV. Being "fed-up" and feeling resentful about one thing or another show a general correlation with the estimate of adaptability, and the severity increases in intensity from Group I to Group IV, being almost negligible in Group I and very marked in Group IV. It is believed that in Chart 9 the estimation of the intensity is of more significance than the percentage of each group having the difficulty, for as has been indicated, similar feelings were present in almost all soldiers in these outfits. It was the extent to which they suffered that was apt to lead to emotional and psychosomatic difficulties.

*Discussion of Symptoms* The symptoms from which the subjects suffered

were clearly related to both their physical status and the difficulties experienced in adjusting to the circumstances which included their chronic illness. An attempt will be made to determine what portion of the symptomatology can be related to the chronic recurring malaria alone, and what to the difficulties in adjustment. It is to be stressed, however, that the illness cannot be differentiated from the

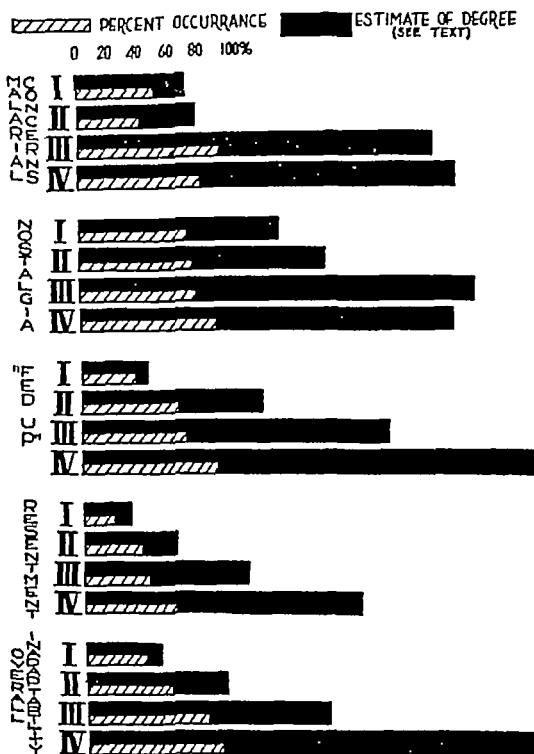


CHART 9 CHART SHOWING PER CENT OCCURRENCE OF CERTAIN EXPRESSIONS OF MALADJUSTMENT AND AN ESTIMATE OF THE DEGREE TO WHICH THESE WERE FELT IN THE GROUPS

emotional reaction to the illness, nor from the reaction to the remainder of the life the patients were leading. The interplay of the reactions was complete. Debility, as well as feelings of hopelessness and concern about the future, lead to apathy and depression. Anorexia, headache, shortness of breath, feelings of faintness, insomnia, are all difficulties which follow upon chronic illness but are also frequent manifestations of neurasthenic and depressive tendencies. If they

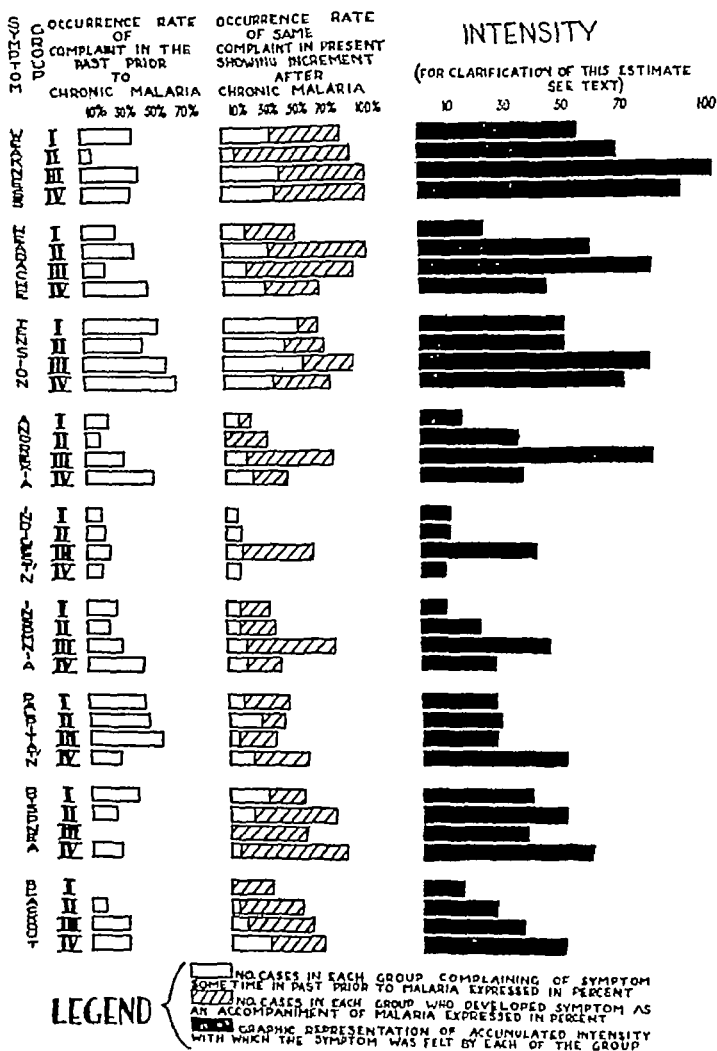
are the result of the malaria alone, they still lead to feelings of ill health and discouragement, and may in turn produce secondary effects upon the individual's morale. Alcoholism is not only a manifestation of inadequate adjustment but it is a precipitant of malarial attacks. Despite these difficulties, the analysis of the symptoms of the four groups permits some general observations to be made, which appear to have pertinence.

It would be anticipated that Groups II and III would have the most symptoms, with Group III showing a slight preponderance, if symptoms were dependent upon physical condition alone. It was the impression of the writers that Group III was slightly more debilitated than Group II, even though no difference could be shown by the various test procedures. On the basis of the analysis of the relative adjustments of the four groups, it would be expected that if adjustment alone were the cause of the symptoms, Group IV would be most severely affected, with Group III but slightly less, Group II markedly less, and with Group I relatively symptom free.

Chart 10 shows the relative frequency of occurrence in each of the four groups of the major symptoms from which the subjects suffered, and the intensity to which the symptom was experienced cumulatively by each group. The first column shows the percentage of patients in each group that had experienced the complaint prior to suffering from malaria. The second column shows the percentage of patients in each group who suffered the symptom at the time of the study, and this is divided by the markings into those who had shown the symptom prior to malaria, and those in which it was a new symptom. The purpose of this was to ascertain whether a symptom was particularly severe for a group because of a predisposition to that type of reactivity. It is to be emphasized, however, that the first column showing occurrence of complaints prior to malaria simply means that the subjects had experienced the complaint occasionally in the past, but not that it was a chronic complaint as it was if charted as occurring after malaria. For example, a large proportion of subjects stated that they had suffered from periods of tenseness when under stress in the past, but this did not mean that they were chronically tense individuals, when calculated in the second column as occurring after onset of malaria, the chart indicates that it had become a noticeable and disturbing symptom that was present very frequently. The intensity of a symptom for a group was calculated by estimating the intensity for each individual, adding them together, and correcting for the number of patients in each group. Obviously, the estimates of intensity of a symptom in an individual was an arbitrary matter, certainly erroneous in individual cases, but believed to afford a fairly accurate picture of the relationship of intensity between the four groups.

It may be noted that there is no constant relationship between the existence of symptoms among members of a group prior to the malarial attacks, and the extent to which the symptom is experienced cumulatively by the group.

Treating all of the symptoms together, it is found that the percentage of occurrence and the intensity increases in the order of Groups I (good physical, well adjusted), II (poor physical, well adjusted), IV (good physical, poorly adjusted)



III (poor physical, poorly adjusted) The relationship of the intensity of the collective symptoms suffered by each group, is shown in Chart 11 Group I, com-



prised of patients who are best adjusted and in good physical condition, has the fewest symptoms, as would be anticipated. Group II, with patients in poor physical condition and well adjusted, has fewer and less intense symptoms than Group IV, in which patients are in good physical condition, but poorly adjusted. In regard to only one symptom, headache, were complaints more frequent and intense in Group II than in Group IV. Group III, which contains patients who are both poorly adjusted and in poor physical condition, has more complaints than Group IV, in which the patients were in relatively good physical states.

The symptoms shown by Group I seem especially worth considering. This group was composed of individuals who were better adjusted than the average, and with few exceptions, displayed less concern and conflict over both malaria and general situational factors than most individuals who had suffered a comparable number of attacks. The difficulties encountered by this group give a fair idea of what might be anticipated in soldiers experiencing an average of 10 attacks of malaria within 12 to 18 months, when psychological factors are minimal. Although they suffered less than the other groups, the complaints were by no means negligible. Eighty-five per cent complained of appreciable physical

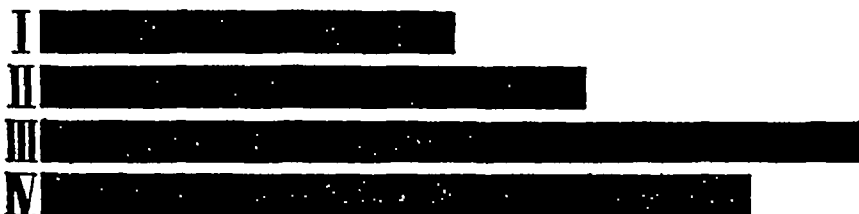


CHART 11 GRAPHIC REPRESENTATION OF THE RELATIVE INTENSITY OF COMPLAINTS IN EACH OF THE FOUR GROUPS OF MALARIAL PATIENTS

weakness, 50% suffered from mild headaches, 50% complained of shortness of breath on exertion, 40% of noticeable and annoying palpitations, a few of insomnia, "blackouts," and anorexia. It is of interest that even in this group, over 60% complained of a moderate degree of tenseness under stress. Nor were the physical alterations induced in them by the recurrent malaria negligible, as has been discussed. They had lost an average of 10 pounds and showed varying degrees of debility. They manifested objectively a degree of fatigability similar to that of the other malarial patients.

The patients in Group II had become more debilitated for reasons which are not apparent and had lost 17 pounds on the average. They were as well adjusted, if not somewhat better adjusted, than the average soldier who had suffered a similar number of attacks. Though more "fed-up" and somewhat more resentful than Group I, there were no indications of difficulties in adjustment earlier in life. However, several in the group had become adequately adjusted only after transfer out of the infantry. The group suffered slightly more from weakness than Group I. Almost every member complained of headaches. Over 70% suffered from dyspnea on exertion, more than 50% from "blackouts" or faintness upon occasions, and more than 30% from anorexia. Insomnia was only slightly

greater than in Group I, and tenseness was no more prominent. The poorly adjusted having been weeded out of Groups I and II, a picture has been obtained which shows what malaria is apt to do, even when adjustment is better than average.

When adjustment is poor there is an appreciable increase in the intensity of symptoms. As would be expected, Group III, containing those in poor physical condition and poorly adjusted, has the most symptoms, but it is of interest that Group IV, comprised of patients in good physical condition, have more symptoms than Group II, in which patients are in poor physical condition. If the reasoning is followed that Group I showed the symptomatology dependent upon recurrent malaria alone with minimal regard to adjustment factors, it may also be supposed that as Group IV was in about the same physical condition as Group I, the difference between the symptoms of these two groups gives an approximation of what part of the symptomatology in Group IV is due to faulty adjustment. Such hypotheses cannot be carried too far, but it is of interest that the relationship of intensity of symptoms between Groups I and IV, also exists between Groups II and III. Group IV (Good physical, poorly adjusted) is worse than Group I (good physical, good adjustment) to approximately the same extent that Group III (poor physical, poor adjustment) is worse than Group II (poor physical, good adjustment), as can be noted in Chart 11. Group III has symptoms that are twice as intense as Group I. This is due both to greater debility and poorer adjustment, and more to poor adjustment than debility, as can be seen from the relationships noted in Chart 11.

A comparison of the groups, symptom by symptom, does not seem justified as the groups are small and the subjective factors which entered the weighing of intensity of symptoms can lead to error. It is noted, however, that the poorly adjusted showed a marked preponderance in regard to weakness and tenseness, and to a lesser extent, of "black-outs." Headaches seemed to depend to a large extent upon debility, for here Group II was more severely affected than Group IV.

The comparison of Groups III and IV is of interest. Although Group III was the sicker, it was not the most seriously affected in regard to all symptoms. The preponderance was most marked in regard to headache, anorexia, indigestion, and insomnia. Group IV suffered more than Group III from palpitation, dyspnea, and "blackouts," which, though they are also neurasthenic in nature, are of a neurocirculatory character, and are less apt to affect the physical condition of the patient. It seems possible that the debility shown by subjects in Group III was due, at least in part, to the fact that they reacted to stress and illness by insomnia, loss of appetite, and indigestion. With 60% of the group suffering from indigestion, and still more from anorexia and insomnia, their recuperation from malarial attacks would be handicapped. However, it is to be noted that Group II, which showed almost as much debility and weight loss, contained but one subject suffering from indigestion.

There developed a clinical impression that although Group III did not have markedly more complaints than Group IV, the subjects were, in general, more seriously affected. It has been seen that the subjects in Group IV tended to-

wards instability prior to malaria and succumbed to stress the more readily. The difficulties due to poor adjustment rested to a larger extent on personality traits in Group IV, whereas in Group III the poor adjustment seemed to a greater extent due to the debility following malaria, and the greater conflict within themselves, as the attitude towards further duty was more ambivalent than in Group IV, where individuals had already given up. The impression seems to have been borne out by the Rorschach Test, which has been discussed among the fatigue studies, and indicates that the apathy, fatigue, and listlessness shown by Group III cut more deeply into the personality structure than the complaints of the other groups.

The attempts at correlation of symptoms with physical condition and personality adjustment, although carried out in broad terms, *indicate that a considerable proportion of the symptoms could be attributed to the recurrent attacks of malaria alone*. However, in individuals who were less capable of adjusting to the circumstances, a very large proportion of the symptoms were due to faulty adjustment. A detailed analysis of personality structure and symptomatology is not possible from the studies and has not been attempted. Situational factors have been stressed more than personality traits, as the study was made of individuals who had been essentially stable, and who had succumbed largely because of the marked difficulties confronting them in the situation. It may be well to note that although the recurrent attacks of malaria caused considerable weakness and debility, soldiers who had adjusted well were, with very few exceptions, still capable of continuing at active service, even if in limited form, whereas soldiers who were poorly adjusted, even when not in particularly poor physical condition, had considerable difficulty in continuing to be useful, and many had become useless for further overseas service.

#### DISCUSSION

Evidence has been presented from the literature that recurrent attacks of malaria, regardless of type, are capable of producing organic damage under certain circumstances, particularly in long standing infections which are inadequately treated. This study of 50 patients who suffered numerous attacks of chronic, recurrent, benign tertian malaria revealed no evidence of damage or dysfunction of the organ systems, measurable by the techniques employed. The studies were thorough, and one of the major purposes of the paper was fulfilled when it was shown that the repeated attacks of malaria and the considerable quantities of atabrine taken by these patients had resulted in no physical impairment other than the debility which was often obvious from inspection. The absence of such changes in our patients is probably due to the fact that they were all young healthy adults who were exposed to reinfection for a period of only six months, and who were all treated adequately and early in their attacks. However, weight loss, weakness, and debility of varying degrees were present in all but a very few of the patients. Fatigability, which was a chief manifestation of their illness, was measurable objectively, and it was considered to be due primarily to the malaria, although other factors entered into its production. Al-

though consistent differences in response to these fatigue tests could be shown between the malarial and control series, individual comparisons were not possible because of the wide range of variation between individual responses. Fatigue, expressed through mental apathy, was demonstrated by the use of the Rorschach Technique to an extent that makes investigation of further use of the test for this purpose seem worthwhile.

The subjects studied presented a characteristic symptomatology which varied in degree from patient to patient. An analysis of the symptoms, which considered all of the various factors involved, led to the conclusion that malaria was the prime factor in their production. However, the individual's adjustment to the malaria and concurrent situational factors, contributed to the development of the symptoms, as well as to their perpetuation and intensification. Regardless of whether the individual's complaints originated in the organic or psychological fields, or both, from a practical standpoint the soldier was of little value to the army once the symptomatology had become fully developed.

The means of preventing the frequent recurrence of malarial attacks, which is of major importance to the prevention of disabling symptomatology, is being investigated extensively by others, and is not the concern of this study. However, the investigation of the asthenia and the symptomatology which has been made in this study has led to the conclusion that the malarial infection, though most important, is but one of many factors which contribute to disabling the soldier from malaria. The soldier is usually capable of remaining useful, even though sometimes in a limited capacity, so long as his morale remains satisfactory, and symptomatology only becomes severe when the adjustment of the person is faulty. It therefore becomes clear that emphasis needs to be placed upon the handling of the person rather than simply of his malaria.

It is not within the scope of the study to review the problem of the maintenance of morale in isolated tropical areas, but the entire topic is of pertinence, for the intensification of the malarial symptomatology through faulty adjustment, just as the incidence of psychoneuroses, bears a direct relationship to the current morale of the units from which the men come. Certain factors, however, seem to be related specifically to the handling of the malarial patient.

Measures by which the development of debility and poor adjustment, conducive to chronic symptoms, can be prevented or controlled are therefore of prime importance. The prominence of concerns over how the malaria might affect their health and future, which arose from ignorance and misconceptions of the disease, suggests that simple, thorough, and uniform instruction can aid in the prevention of a neurotic reaction. Instruction which does not attempt to minimize the dangers of the infection, or to exaggerate the efficacy of present therapy, as far as cure is concerned, has been most satisfactory. Patients were told that the attacks of malaria would continue to recur, but that the disease is self-limited, and attacks would become extremely rare after two to three years, in the case of benign tertian malaria (41), (42), (43). For the most part men were capable of accepting reality. It was concern over a life time of chronic ill health that depressed them. The doctor treating the illness must bear in mind that the

soldier may have heard all sorts of conflicting reports and rumors concerning malaria and the ill effects of atabrine. It was noted that line-officers, particularly well informed in regard to what malaria might do to their men and what could be expected from a soldier suffering from recurrent attacks of the disease, were able to utilize their men more effectively.

There were no indications that the stresses of malaria required better physical health than the standards established by the army for overseas service. However, this study has shown that maladjustment to the stresses of the illness, and the difficulties of life in this area, played a major rôle in the incapacitation of soldiers from malaria. Soldiers who have adjusted poorly in civilian and military life, and to overseas service, are very likely to make a poor adjustment to malaria, and become incapacitated rapidly. Experience taught that those soldiers who developed chronic symptoms early in the course of their disease, particularly such debilitating ones as anorexia, indigestion, and insomnia, should be removed from units where marked physical exertion is required. If they remain, inability to perform full duty leads to debility, discontent and discouragement which is not only harmful to themselves but is detrimental to the "malarial morale" of their units. The entire reaction of the soldier to his illness, rather than such specific and infrequent findings as splenomegaly and anemia, should determine future duty status. Clearly some men could no longer be utilized overseas, but frequently men who were transferred early to well delineated duties commensurate with their capacities did extremely well and lost many of their chronic symptoms. This enabled the soldier to feel that he was an integral part of an organization, to maintain pride in accomplishment, and provided opportunity for promotion.

The deleterious effects of repeated and prolonged hospitalizations have been discussed. Minimal hospitalization reduced the tendency towards the development of neurotic patterns. The hospital area proper, when containing many patients about to be returned to the United States, as well as numerous psycho-neurotic casualties, is unsuited for satisfactory convalescence. Individualization of treatment directed towards reassurance regarding physical status, further malarial instruction, and to creating in the individual a sense of responsibility and a desire to return to his unit as soon as possible, was helpful. The rehabilitation of the patients studied had been hampered in the past by the lack of recreational facilities, their isolated and monotonous existence, and the duration of their stay in the tropics, without prospects of returning home before termination of the war. The marked alteration in attitude, with alleviation of complaints, that followed the announcement of the army rotation policy, emphasized the important need of these men to have a more meaningful and satisfactory future in prospect.

#### SUMMARY

1) Fifty soldiers, who had suffered an average of 10 recurrent attacks of benign tertian malaria over a period of approximately one year, were studied to deter-

soldier may have heard all sorts of conflicting reports and rumors concerning malaria and the ill effects of atabrine. It was noted that line-officers, particularly well informed in regard to what malaria might do to their men and what could be expected from a soldier suffering from recurrent attacks of the disease, were able to utilize their men more effectively.

There were no indications that the stresses of malaria required better physical health than the standards established by the army for overseas service. However, this study has shown that maladjustment to the stresses of the illness, and the difficulties of life in this area, played a major rôle in the incapacitation of soldiers from malaria. Soldiers who have adjusted poorly in civilian and military life, and to overseas service, are very likely to make a poor adjustment to malaria, and become incapacitated rapidly. Experience taught that those soldiers who developed chronic symptoms early in the course of their disease, particularly such debilitating ones as anorexia, indigestion, and insomnia, should be removed from units where marked physical exertion is required. If they remain, inability to perform full duty leads to debility, discontent and discouragement which is not only harmful to themselves but is detrimental to the "malarial morale" of their units. The entire reaction of the soldier to his illness, rather than such specific and infrequent findings as splenomegaly and anemia, should determine future duty status. Clearly some men could no longer be utilized overseas, but frequently men who were transferred early to well delineated duties commensurate with their capacities did extremely well and lost many of their chronic symptoms. This enabled the soldier to feel that he was an integral part of an organization, to maintain pride in accomplishment, and provided opportunity for promotion.

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# EXPERIMENTAL EPIDEMIOLOGY

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## PART I PHENOMENA OF EPIDEMIOLOGY

### EXPERIMENTAL EPIDEMIOLOGY

Study of epidemiology, the mode of spread of communicable diseases in herds of human beings or animals, has focused for 3,000 years on the following everyday problems—*Causation* what initiates epidemic sickness, *reservoirs* where do epidemic sicknesses originate, *transmission* how is this sickness brought to and distributed throughout the herd, *resistance (immunity)* which individuals of the herd will escape or survive the sickness, *termination* what brings epidemic sickness to an end? Much has been learned, much remains mysterious.

Knowledge of epidemic sickness can be divided into that which accrued during a) the pre-experimental period, before 1876, b) the period of experiment on infection in the individual, 1876 and later, and c) the period of experiment on infection in the herd, 1920 and later. Knowledge in each period can be further classified according to its bearing on the above questions of causation, reservoirs, transmission, resistance, and termination.

During the first, the pre-experimental period, certain sicknesses came to be regarded as communicable, their prevalence was described in an orderly manner, and their causation guessed at in terms of minute, specific, living organisms. Briefly, ideas and events occurred chronologically somewhat as follows (Table I). From earliest times people distinguished between certain kinds of illness—pox, for example, and rabies. Then, too, they noted that at certain times and in certain places a given sickness was more or less prevalent. Of most importance, however, was the fact that they regarded certain diseases as communicable and hence rigorously, and often cruelly, shunned or isolated those afflicted or those coming from an epidemic area. The books of Hippocrates written in the Fifth Century B.C. contain the author's own observations on different types of sickness and on fluctuations in their prevalence, together with his conclusions that individuals and populations differ among themselves and undergo changes in their resistance to certain sicknesses. Finally, he regarded epidemics as the results of three sets of circumstances: changes in the resistance of populations, alterations in their immediate environment, and variations in the atmosphere. Meanwhile, from ancient religious sources and from astrologers came

<sup>1</sup> Dr. Webster was engaged in a preparation of this summary of his results and views, when death interrupted the undertaking. Part I was completed and, with very few changes, is presented as he left it. For Part 2 Dr. Webster left notes and working sheets which clearly indicated its pattern. This material, together with Dr. Webster's notes on the

TABLE I  
Chronological Survey of Knowledge of Epidemics

PERIOD	DATE	SOURCE	TOOLS	SICKNESS IN THE INDIVIDUAL			SICKNESS IN THE HERD					MISCELLANEOUS OBSERVATIONS ON EPIDEMIC SICKNESS
				Cause	Source Transmission	Resist- ance (Immun- ity)	Cause	Source Transmission	Epidemic curve	Resist- ance (Immun- ity)	Termi- nation	
A Pre-experi- mental	Earliest times	General population	Observation		Communi- cability			Communi- cability				Different types of sickness Fluctuations in prevalence Different types of sickness Fluctuations in prevalence
	500 B C	Hippocrates	Observation	Environ- ment de- presses re- sistance of individual			Environ- ment de- presses re- sistance of population					Quarantine established Prevalence described quantitatively
	1540 A D	Frascastorius	Observation	Living mi- croorgan- ism			Living mi- croorgan- ism					Classification on specific etiology
	1662 1682	Graunt Farr	Observation									Types of epidemics
B Experimental infection in the indi- vidual	1876 1890	Koch School	Experiment	Specific living agent proved	Communi- cability proved	Healthy carri- ers	Specific living agent	Food, water, animals, insects, man				
	1890	Bacteriolo- gists	Observation Experiment		Food, water, animals, insects, man		Fluctuating virulence		Fluctu- ating viru- lence	Immun- iza- tion	Fluctu- ating viru- lence Immun- iza- tion	
	1890	Epidemiolo- gists	Dialectics									
C Experimental infection in the herd	1920	Topley Webster	Experiment									Experimental production and study of epidemics

pronouncements that epidemics were caused by angry gods or by meteorological configurations. To these observations and theories nothing noteworthy was added for 2,000 years. In 1546, however, Fracastorius published a treatise on contagion in which he set forth the theory, on the basis of his own studies of syphilis and other so-called communicable illnesses, that sick individuals harbored a living specific microorganism which was transferred to other individuals causing each in turn to develop that same illness. Meanwhile, the idea of communicability had become so widely accepted by the laity that fourteen illnesses were so characterized and quarantines against them were established in seaport towns. From that time forward, communicability and infectiousness of certain ailments received increasing attention. Finally, and perhaps of most importance, in this period came Graunt's collection and tabulation of vital statistics, and Farr's later application of statistical mathematics to vital statistics to furnish a quantitative description of mortality and morbidity rates. Thus, in this pre-experimental period, the beginnings of clinical classification of sicknesses, the foreshadowing of establishment of the infectious nature of certain diseases, and the development of a precise method for describing disease prevalence among populations may be noted. We are left, however, with little notion as to the causes, reservoirs, transmission, resistance to, and termination of epidemics beyond the credible guesses of Hippocrates.

During the second period, that of experiment on infection in the individual, the specific causal agents of certain sicknesses were proved to be living microorganisms and much was learned concerning their source, mode of transmission, and ability to immunize. Two types of epidemics were recognized and the genesis of one became clear. This period will now be examined in more detail.

Following Leeuwenhoek's discovery of the compound microscope, which enabled one to see minute objects, many workers described living microorganisms under all sorts of conditions. But by 1820 Bassi had demonstrated fungi obtained from silkworm muscardin and all but proved their etiologic rôle. Forty years later, Davaine had observed microscopic rods in the blood of animals with anthrax and had shown that blood containing these rods, when injected into animals, was capable of reproducing the disease, but that blood which did not contain the rods, when so injected, did not produce anthrax. Of crucial significance, however, was the demonstration by Koch, in 1876, of the means by which microorganisms might be grown apart from the body in pure culture. By inoculating such pure cultures of microorganisms into animals, observing the resultant characteristic disease, culturing the same organisms from the diseased tissue, and, finally, reinoculating this second culture into animals with similar results, he proved conclusively the etiologic rôle of the given agent. The successful carrying out of these procedures came to be known as the fulfillment of Koch's postulates for testing the etiologic rôle of a given agent. One after another were discovered the bacilli of anthrax, tetanus, tuberculosis, and diphtheria, the cholera vibrio and the cocci of meningitis and pneumonia. Then Loeffler and Frosch found that foot and mouth disease could be transmitted by materials passed through fine filters which removed all visible material and left nothing

which could be grown by ordinary methods. These agents came later to be classed as viruses. Meanwhile, Koch's technique made it possible to trace pathogenic organisms to various reservoirs and to follow them from the reservoir to the new host by means of the vehicles of food, water, insects, etc. Finally, Koch showed that not all individuals exposed to cholera vibrios developed the disease but, on the contrary, that some carrying the agent in their tissues remained well. Pasteur showed further how animals could be immunized against a pathogenic agent by first treating them with attenuated cultures of the same agent.

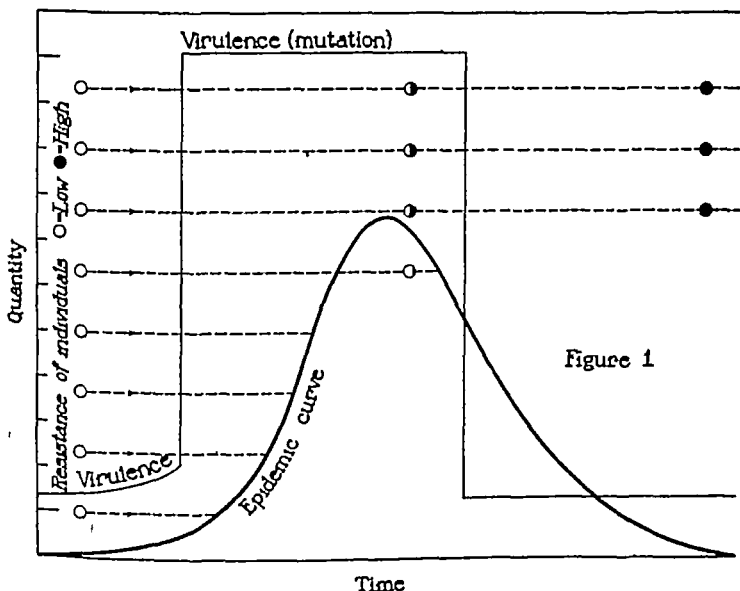
This knowledge led far toward an understanding of infection in the individual. The basic fact may be stated as follows: that certain sicknesses are caused directly when a specific microorganism comes into contact with a susceptible individual. Why some individuals so exposed contract the characteristic illness while others escape remains an enigma. Is this circumstance due to differences in the virulence or dose of organisms encountered, or to a previous immunization experience, or perhaps to some other factors not yet explored?

This bacteriological knowledge has led also to a better understanding of infection in herds. In most instances in which the mechanism of infection in the individual is well understood, it is likewise plain in the herd, and vice versa. In due course two general types of epidemics became recognizable: Type 1 which occurs in susceptible populations exposed for the first time to a virulent microorganism, and Type 2 which occurs in populations in which the virulent microorganism is already established. An example of the first type is an outbreak of typhoid following ingestion, by a previously unexposed population, of contaminated food, milk, or water. Here not only is the specific cause of the epidemic clear, but the reservoir and mode of transmission of the agent can be determined. What remains vague, however, is why some of these individuals become ill, even fatally, whereas others are mildly attacked or escape altogether. And, lastly, why does the epidemic come to an end although so many exposed persons remain healthy? Did the virulence of the agent change, did certain fortunate individuals become immunized during the early stages of the epidemic, or are other factors, not yet recognized, involved?

Examples of the second type of epidemics are the seasonal outbreaks of measles, whooping cough, poliomyelitis, yellow fever, and malaria. Indeed, most of the infections which plague man today behave in this manner. In this group a great deal is known about the nature of the specific agents, their reservoirs, their mode of transmission, and their immunizing properties. What remains to be solved is the problem of why a relatively quiescent parasite suddenly spreads throughout a population, inciting a vastly greater number of cases of illness, and of greater severity, than ordinarily. In other words, the causation of epidemics in the second class is not clear. Nor are the reasons plain for their termination and their selection of victims.

Early in the Twentieth Century theories were formulated to answer the foregoing puzzling questions about epidemics. Epidemiologists, noting that bacteriologists could reduce the virulence of disease-producing microorganisms by prolonged cultivation on certain laboratory media, and often restore it by repeated animal passage, reasoned that in Nature, too, virulence must fluctuate

and hence they arbitrarily attributed the rise and fall of epidemics in already infected populations (Type 2) to changes in the virulence of the specific agent. Indeed, the very shape of the epidemic morbidity or mortality curve was regarded as a resultant of the progressive rise and fall of virulence. Then, too, epidemiologists, noting that animals can be successfully immunized in the laboratory by repeated injections of small doses of pathogenic microorganisms, reasoned that the same events must occur during epidemics. Hence they postulated that epidemics (Types 1 and 2) are terminated not only because of a loss in virulence of the agent but because of immunization of a part of the population through chance



TEXT FIG 1. DIAGRAM REPRESENTING MECHANISM OF EPIDEMICS ACCORDING TO CURRENT THEORIES

(The broken, horizontal lines indicate the fate of individuals in the epidemic)

exposure to small doses of the agent. This immunization process was thought to account in part for differences in the fate of individuals during epidemics—those who succumbed had encountered highly virulent organisms, and those who resisted, less virulent organisms in small doses, thus becoming immunized (Text-Fig. 1). These explanations of epidemics drawn from experiments on individual rather than herd infection remained firmly entrenched until the advent of experimental epidemiology in 1920.

The third period of epidemiological knowledge, that of direct experiment on infection in animal herds, was ushered in by W. W. C. Topley in his Goulstonian Lecture of 1919 (1). That he accepted at the outset the current theories of epi-

demiology is clear from his conclusions, " we are thus left with a conception of the virus of a given disease being distributed fairly widely throughout the world as an apparently harmless parasite on the human host, but taking on during epidemic periods a new and sinister rôle, only to relapse again into comparative quiescence as the epidemic subsides" Again he states, "while there seems little room for doubt that increased pathogenicity of the parasite must play an essential part in the rise of the wave of disease, it is much more difficult to decide on the relative importance of variations in the powers of parasite and host in bringing about its decline" These views, however, have undergone a radical change as experimental data have accumulated

Topley then stated what we consider to be the fundamental viewpoint of experimental epidemiologists "In any attempt to obtain information on such points as these by experimental observation it is clearly necessary to work with some organism which is known to give rise to epidemic disease among the animals utilized" And again in 1921 he states (2) "The experiments here reported form

TABLE II  
*Types of Experimental Epidemics*

NAME	SPECIFIC MICROORGANISM			POPULATION	
	Pathogenicity	Infectivity	Persistence		
Type 1	+ → +++	—	—	Previously unexposed	
Friedländer—Mouse (a)	+++	+++	±	"	"
Pneumococcus—Mouse (b)	++	+	0	"	"
Salmonella—Mouse (c)	++	++	+++	"	"
Pasteurella—Rabbit (d)	+	+++	+++	"	"

Other Examples

Fowl Pasteurella—Mouse (1a)

Rabbit " " (1b)

Fowl " Fowl (1d)

the preliminary steps in an attempt to *investigate the laws which govern the spread of bacterial infection among an animal population, by observations carried out under conditions which are as far as possible experimentally controlled*" The basic procedure was and has continued to be the experimental induction of epidemics of some native infection among populations of small animals

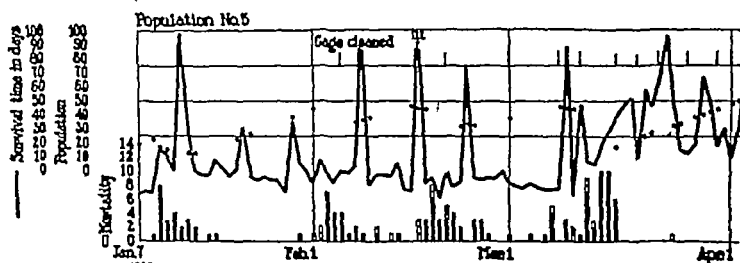
The experiments in epidemiology covering a period of 20 years are readily divisible into those which concern a) the development of working models of epidemics, b) the study of the mechanisms governing spread of infection in these working models, and c) the organizing of the resulting experimental data .

*Working models of simple epidemics in hitherto unexposed populations* have been set up with a number of representative pathogenic agents (Table II) The most classic models were obtained by using microorganisms of high pathogenicity and infectivity Such organisms, however, failed to survive in the population and to carry on the infection *Epidemics produced with these agents of high pathogenicity and infectivity but low persistence are designated Type 1a* The following experi-



ments illustrate the sort of epidemic which follows the introduction of Friedländer like organisms into populations of susceptible mice

This organism had been observed to spread readily among certain experimental mouse populations and to give rise to highly fatal pneumonias (3) Thus, in September, 1925, epidemics of pneumonia occurred "spontaneously" and abruptly in three of four experimental populations of mice under observation Each epidemic was characterized by an explosive onset, a rapid increase in number of deaths to a peak followed by an abrupt decline, and a subsequent period of very low death rate The epidemic mortality curves tended to the bell form, more than 50 per cent of each population succumbed (Text-Fig 2) A Friedländer like organism was recovered in pure culture from nasal passages, lungs, and blood of fatal cases and from sick mice The source of this infection was never determined but was suspected as being the caretaker who suffered from chronic sinusitis and from whom the same organism was recovered



TEXT-FIG 2 "SPONTANEOUS" EPIDEMIC OF *B. FRIEDLÄNDER* IN MICE

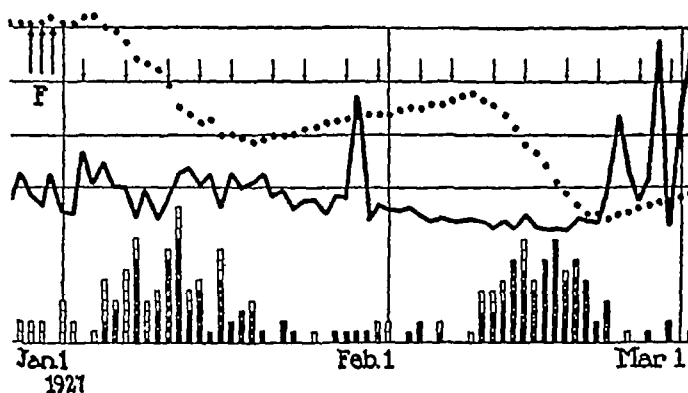
We produced epidemics of this Friedländer like pneumonia experimentally among populations of previously unexposed mice by introducing a small number of carriers in the following manner

*Experiment A*—On November 5, 1926, a population of healthy mice was set up by assembling ten Rockefeller Institute mice in a large standard cage and adding two healthy individuals daily thereafter On December 29, with the population numbering 101 mice, two healthy immigrants received a nasal instillation of 0.03 cc of broth containing approximately 100 Friedländer bacilli This strain (No. 18) had been isolated from the nares of a carrier midway between two epidemics and was designated, therefore, as an inter-epidemic strain On two succeeding days, the two immigrants received similar treatment, so that a total of six infected mice were added to a population of 101 normal animals Subsequently two healthy mice were added daily to the population

The results of this experiment are shown in Text-Fig 3 The "experimental carrier" immigrants died 5, 35, 15, 15, 9, and 50 days respectively after instillation of the Friedländer bacilli Meanwhile, the infection spread rapidly to the healthy population The number of daily deaths increased quite regularly to a peak of thirteen on January 12 By January 19, 15 days in all, 88 mice had died

and the population, including subsequent daily immigrants, was reduced to 46. Throughout the epidemic the dead mice showed the typical Friedländer bacillus lesions and yielded the organisms mostly in pure culture. Following this epidemic a quiescent period ensued, during which time the immigrants increased the total population to 69. Then a second outbreak occurred, reaching its peak on the 5th day with the death of ten mice, and lasting 13 days, with a total mortality of 85. Subsequently mortalities ceased and the immigrants increased the population census from a low level of ten to 94. No further Friedländer outbreaks occurred and the infection disappeared.

*Experiment B*—On February 18, 1927, Experiment A was repeated in duplicate. Two groups of 100 healthy Rockefeller Institute mice were each placed in standard cages. They were observed for 33 days and remained healthy except for losses by fighting, which were replaced. On March 23, twelve additional mice



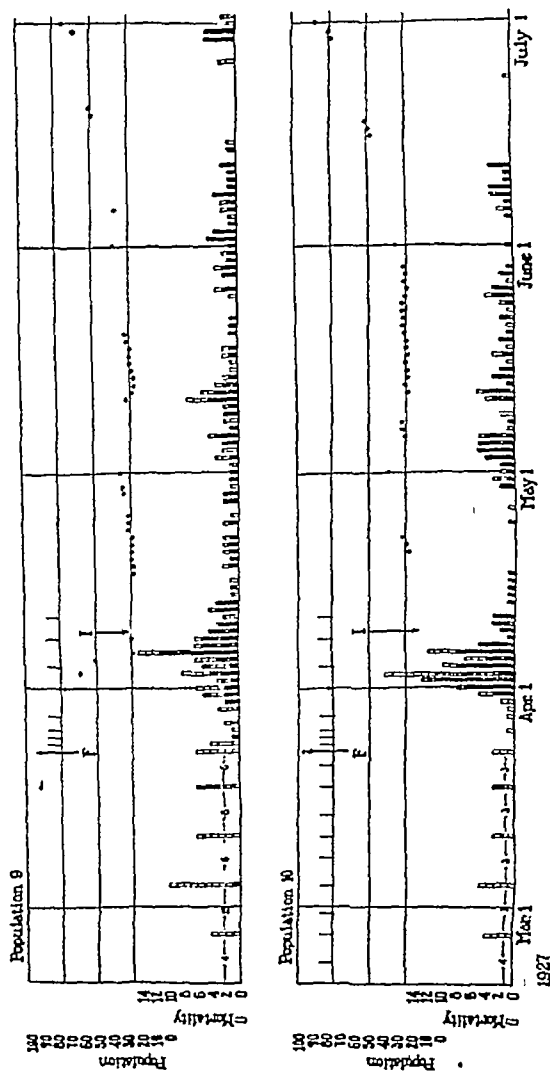
]-1 mouse dead, date of death uncertain within 6 day period

□-1	.	.	.	no autopsy
◐-1	.	.	.	autopsy findings negative
▨-1	.	.	.	Bact. friedlander
■-1	.	.	.	Bacteritidis
◻-1	.	.	.	Lathrop mouse
?	-	-	-	No mice added

TEXT-FIG 3 (EXPERIMENT A) EXPERIMENTAL EPIDEMIC OF *B. FRIEDLÄNDERI* IN MICE

each received a nasal instillation of 0.03 cc. of broth containing about 100 Friedländer organisms, strain No. 18. Six of these mice were then added to one population (No. 9) and six to the other (No. 10). Four days later deaths occurred amongst the inoculated immigrants and explosive outbreaks of great severity took place in both communities. Within 3 weeks, 80 to 90 per cent of each population had succumbed to Friedländer pneumonia. At about this time, daily immigration of two healthy mice per population was commenced. The infection smouldered in endemic form but finally, after 2 to 3 months, disappeared completely (Text-Fig. 4).

These experimental epidemics of Friedländer pneumonia in hitherto unexposed populations simulate closely those which had been observed to occur "spontaneously." They illustrate, moreover, one of several ways in which pathogenic microorganisms affect populations when they gain access for the first time. The



TEXT FIG 4 (EXPERIMENT B) EXPERIMENTAL EPIDEMICS OF B. FRIEDLANDER IN MICE

highly pathogenic Friedländer bacilli spread rapidly throughout the susceptible mouse populations, giving rise to highly explosive, fatal epidemics, but failed to become established in survivors. An analysis of factors responsible for the various features of these epidemics follows later.

Another sort of epidemic syndrome is observed when a microorganism of high pathogenicity is brought into contact with a hitherto unexposed population in which it has little or no natural tendency to spread or persist, unless certain factors are properly modified (Type 1b). Illustrative of this situation are experiments on pneumococcus Type III epidemics in mice.

Pneumococci from human sources are known not to spread readily from one mouse to another by contact, nor do they generally prove fatal, when inhaled, unless special measures are taken, such as injections of alcohol. But certain pneumococci do prove fatal to mice when instilled into the nasal passages in the following manner.

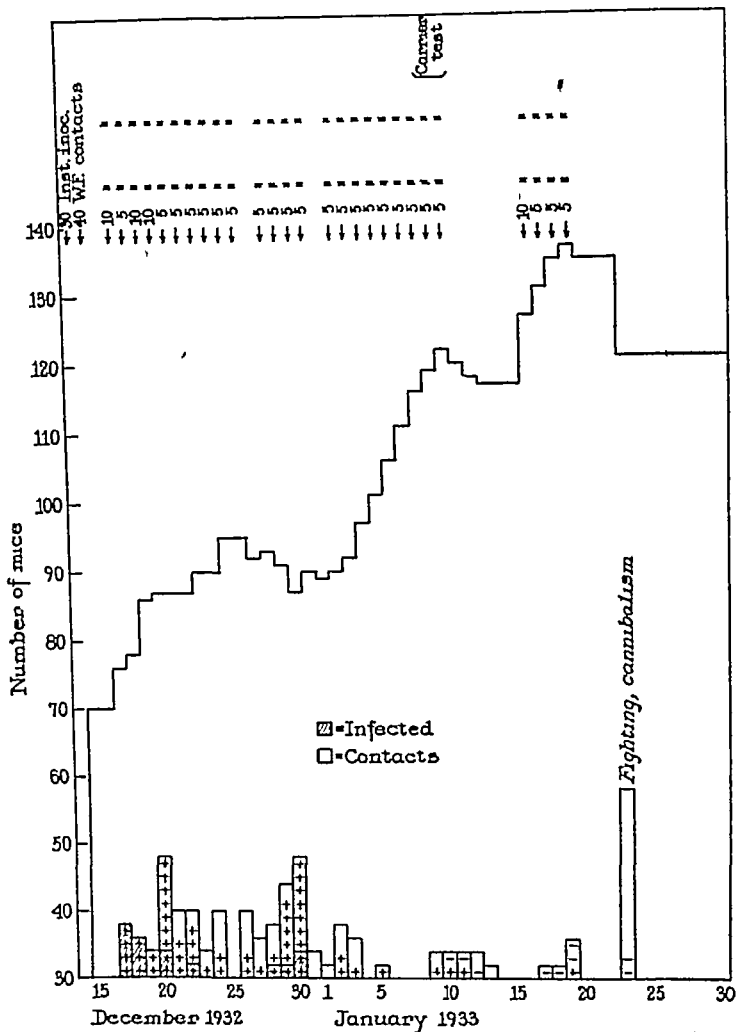
Fifty strains of pneumococci isolated from human cases or carriers within 72 hours of test were grown for 18 hours in broth and diluted so that 0.03 cc. of suspension contained about 150,000 organisms.

0.03 cc. was instilled intranasally into twenty Rockefeller Institute mice 3 months of age. They were then placed in individual jars. Tests of ability of pneumococci to spread from nasally infected individuals to contacts were made by placing ten mice infected intranasally into a single cage, and 6 to 48 hours later adding ten healthy, un inoculated mice, and one or two additional healthy mice each day thereafter. Nasal carrier tests were made on the entire population at frequent intervals and bacteriological tests on mice dying during the period of observation. The results of 69 titrations of 50 strains showed Type III pneumococci, especially those from cases of pneumonia, to be high in intranasal virulence and in tendency to spread to healthy contacts. 21.5 per cent of the Type III strains were low in nasal virulence, however, and individual strains showed marked differences.

These results led us to study many Type III strains and finally to select those with the highest nasal pathogenicity and tendency to spread. These strains were then tested for their ability to incite epidemics among young mice of highly susceptible strains (4). Of more than twenty tests, only a few showed explosive, highly fatal epidemics. In no test did the pneumococci persist in the population. The following protocol illustrates the more explosive form of epidemic.

*Experiment C*—On December 14, 1932, thirty Rockefeller Institute mice were each given a nasal instillation of 0.03 cc. of broth containing approximately 150,000 pneumococci, Type III. On December 15 they were added to a population of forty healthy mice of the highly susceptible white-faced strain. Two days later, ten healthy immigrants were added, on the following day, five, on each of the next 2 days, ten, and five daily thereafter (Text-Fig. 5).

On December 17, four of the infected mice died and showed pneumococci, Type III, in pure culture in blood and lungs. Three died on the following day with similar findings. Altogether and within 17 days, fourteen of the thirty infected mice died—46.6 per cent. The survivors, although tested later for carriers, remained free of pneumococci.



TEXT FIG 5 (EXPERIMENT C) EXPERIMENTAL EPIDEMIC OF PNEUMOCOCCUS, TYPE III, IN MICE

On December 19, two of the healthy mice died with pneumococcus pneumonia, on the following days, seven, five, four, two, and five respectively. The epidemic

among the healthy mice declined after 22 days, but not until 60 mice had succumbed, mostly with proved pneumococcus, Type III, pneumonia. Thereafter the mortality became sporadic and ceased after another 20 days. Nasal carrier tests were made but no pneumococci were recovered. Shortly thereafter the experiment was discontinued.

*Clear-cut working models of simple epidemics in hitherto unexposed populations (Type 1)* were first set up in our laboratory (1930). Previously Topley had devoted his attention to events in infected populations following the addition of susceptibles and Amoss had done the same thing aside from his original experiment. Thus the epidemics developed by Topley as well as those by Amoss must be considered as Type 2, because they involved previously exposed populations. In this instance, two cages of five mice each were fed *B. typhi-murium* and placed midway in a row of twenty cages each containing five healthy mice. In the next 23 days, six of these fed mice died of mouse typhoid and six of the 100 contacts. On the 32nd day, forty more cages each containing five healthy mice were placed on adjoining shelves. Seventy days later, 62 per cent of the original contacts and 50 per cent of the subsequent contacts succumbed to mouse typhoid (5). The experiment had drawbacks in that mortality curves were plateau-, rather than bell-shaped, the supposedly healthy populations were actually not free from typhoid, and the spread of infection from infected to healthy animals depended entirely on the vagaries of the attendant.

A graph showing the time distribution of deaths was similar in every way to graphs showing mortality among populations of mice in which mouse typhoid was spreading spontaneously (Lynch) (6). In 1930 we showed that if a few mice given an intranasal instillation of mouse Friedländer pneumonia bacilli are placed in a cage with 100 normal mice, an epidemic results similar to spontaneous outbreaks observed in like populations (Text-Fig. 3). Finally, we showed that Class 1 epidemics could be induced by administering to each individual constituent of a population a fixed dose from a single culture of organisms. This was accomplished with proper doses of mouse typhoid and mouse Friedländer pneumonia organisms. It was noted that the mortality curves following this experimental infection of individual mice were similar to those which resulted when infected and normal mice were brought together, and likewise similar to the mortality curves following spontaneous outbreaks.

In each of these models the cause, reservoirs, and transmission are known. What accounts for the shape of the epidemic curve? Clearly, in the case of the epidemic following experimental infection of individual mice, fluctuations of virulence and dosage are ruled out since they are experimentally fixed. It is not unlikely that virulence and dosage are constant when normal mice are brought to an infected herd and when infected individuals are introduced into a normal herd. We are left, then, with one known variable to account for the shape of the curve—differences in the power of individuals to resist the invading agent. At this point in the argument, we postulate that the shape of the model curves of Class 1 epidemics does, in fact, describe the individual differences in resistance of the population exposed.

Models of Class 2 epidemics have also been readily produced experimentally by adding fresh, susceptible recruits to an already infected population. In 1921 Topley fed mice a 10 year old laboratory strain of *B. enteritidis* mouse typhoid, transferred them to a suitable cage, and added fresh mice thereafter. Additions were made at different rates in three such tests and the spread of mouse typhoid was observed. In each experiment an intercurrent infection with mouse typhoid bacilli of another serological type marred the otherwise clean-cut nature of the experiment but the significant finding remained, that the addition of immigrants to each population was followed by a succession of wave like, enteric epidemics and the discontinuance of additions brought the epidemics to an end. Amoss, in 1922 (5), assembled batches of healthy mice in a series of small cages and in their midst placed two boxes of mice fed on mouse typhoid bacilli. The attendant was then allowed to spread the infection. About a month later, 200 mice in forty cages were added to the population. Following this an epidemic of mouse typhoid occurred fatal to at least 50 per cent of the mice. The time distribution of deaths was similar to that encountered by Lynch in her observations on spontaneous epidemics of mouse typhoid. The surviving population was then recruited to its original numbers, following which another severe epidemic occurred fatal to 70 per cent of the entire population. A second and a third replacement were followed by outbreaks of decreasing severity. These tests were followed by others by Greenwood and Topley (1925) (7) who showed that the repeated addition of fresh mice to populations infected with *Pasteurella* is followed by recurring epidemic waves. Finally, Webster (1930) (8) showed that if immigrants were added to one of three mouse populations infected with mouse Friedländer pneumonia bacilli, recurrent epidemics ensued, whereas if at the same time and under identical conditions, addition of immigrants was discontinued in the two remaining populations the Friedländer infection died out. There is no doubt, therefore, that epidemics may be incited in already infected populations by the addition of fresh recruits and that epidemics may be terminated by the discontinuance of recruits.

The effect of adding recruits to infected populations was examined further. Topley (1921) (9) and later Greenwood and Topley (1925) (7) noted a relationship between amount of immigration and amount of mortality. Thus, they later compared six infected populations for  $7\frac{1}{2}$  months to determine the effect of immigration rate upon amount and distribution of mortality. Unfortunately, no two populations were kept under identical conditions and no two were experiencing the same type or types of infection at the same time, and Greenwood and Topley agree that the evidence cannot be regarded as crucial. Yet, the data do suggest the possibility that a relatively high and constant immigration rate is associated with a relatively high death rate, a short inter-epidemic interval, and a regular form of epidemic curve. Later, we observed that in four populations of mice maintained simultaneously under identical conditions, infected with Friedländer pneumonia, and increased by recruiting two mice per day, epidemic waves occurred at a definite population level, lasted a definite number of days, and reduced the census to a definitely low level. Moreover, when mouse typhoid was

spreading in similar communities, the mortality waves occurred at 9- to 11-day intervals. All this suggests that the form, as well as the occurrence of the epidemic waves, may depend upon the rate of immigration of fresh individuals.

Having successfully produced models of Class 2 epidemics, we are ready to attack the five main problems again. The causation of these epidemics, beyond the fact that it is in some way bound up with the business of adding immigrants, remains unknown. Do the immigrants cause an increase in virulence of the agent or an increase in dosage, do they increase the susceptibility level of the population or act in some other unknown manner? The reservoir of the infection is known to be individual animals already in the population, and the mode of transmission, contaminated food. What determines the shape of the epidemic curve—fluctuations in virulence or dosage of the agent, or changes in susceptibility of the population? What terminates the epidemic—a progressive drop in virulence or a progressive increase in resistance of the population due to weeding out of susceptibles or to immunization of a percentage of constituents? The questions thus far remain the same for experimental epidemics as for similar epidemics in Nature and likewise remain unanswered.

In previous paragraphs we traced the history of knowledge of the spread of contagious disease in the herd through the pre-experimental period, the period of experimentation on infection in the individual, up to the period of experimentation on infection in the herd. There we showed how models of the two chief classes of epidemics may be produced experimentally and noted that in the main the same questions remained for answer in the model epidemics as in natural epidemics. We propose now to describe experiments illustrating how some of these problems were attacked.

Since epidemiologists have emphasized that virulence fluctuates and is responsible for most of the phenomena of epidemics, it became important to study the virulence of specific agents. Topley said (1919) (1) "The point, then, which it seems necessary to determine is whether a series of natural passages will indeed lead to the evolution of strains of the parasite especially well-equipped for producing disease on the epidemic scale, and whether there is any reason to believe that continued variation along the same lines will result in such modifications as will render it less likely to infect new hosts." He then found on experiment that a series of intraperitoneal passages of strains of mouse typhoid led not to an increase but to a decrease in virulence, as Danysz had previously noted. He thought that strains taken from sick mice were more virulent on intraperitoneal injection than strains taken from dead mice. He then stated that he was not justified in assuming that such results represent what happens when passage occurs under natural conditions and proceeded to feed cultures to small lots of mice and to add recruits. Mice added during the early stages of the epidemic, he found, largely succumbed, whereas those added later showed an increasing tendency to escape and, in some cases, all survived. He then offered "one inescapable conclusion," namely, that "the cessation of the epidemic is actually due to the loss, on the part of the parasite, of the power to infect fresh individuals." Further on he stated that the essential phenomena of an epidemic may be the prog-



ress of the virus through a cycle of selective variations which must be reversed in each successive wave. And, finally, he remarked that "the cycle of variation passed through by the parasite during an isolated attack of disease is very similar to that traversed by the same bacterial virus during an epidemic wave."

At this point we commenced our studies in experimental epidemiology and spent the first years in developing what we think is a satisfactory technique for measuring virulence and, indeed, dosage and resistance of the host as well. At the outset we agreed with Topley, that artificial injections of bacteria into animals do not measure bacterial and host factors as they operate in Nature. Therefore we perfected techniques for measuring these factors under natural conditions. In the case of mouse typhoid, animals were given a numerically measured dose of organisms from a single (often single-cell) culture into the stomach by tube. When response to pneumonia producing organisms was tested, fixed doses were instilled intranasally. These procedures were followed by an incubation period similar to that in the spontaneous disease, by an amount and distribution of sickness and death, and by lesions entirely comparable with those in the natural disease. We regard this procedure, therefore, as an accurate measurement of virulence, dosage, and host susceptibility.

Let it be noted at once, however, that as in Nature, the response of animals is not uniform. Some die promptly after the minimum incubation period of 6 days, others succumb at varying periods up to 30 days and sometimes longer. The all-important point, however, is that this group response is regular and predictable if, and only if, batches of twenty or more properly controlled mice are employed. Mice purchased from dealers, of unknown age, maintenance and dietary experience, and frequently infested with parasites or other infectious agents have not given predictable results in our hands or in Topley's. Fortunately we decided at the outset to effect every control possible of the mice or host factor and hence bred our own animals under standard conditions at the Rockefeller Institute. Consequently we achieved satisfactory results, whereas Topley depended during the early years of his work on purchased mice and artificial methods of measuring virulence.

We have compared the virulence of mouse typhoid cultures obtained from the blood of acute cases of mouse typhoid just before death, and from the stools of healthy survivors and found no differences. The same results were obtained when blood and nasal carrier strains of Friedländer pneumonia organisms were compared. We have passed mouse typhoid cultures rapidly through mice intraperitoneally, using a blood culture for passage, and by mouth, using stool cultures, and have found no change in virulence. The same has been done with Friedländer organisms intranasally. The virulence of thirty strains of fowl cholera obtained at autopsy from fatal cases of the spontaneous disease was compared with that of thirty nine strains cultured from the throats of healthy carriers, with a slight difference in favor of the autopsy strains.

The most important titrations, however, were carried out on cultures of organisms recovered from populations during various epidemic and endemic phases of infection. Comparative titrations have been made on strains from epidemics

of pasteurellosis in rabbits and in chickens, as well as in mice. Similar titrations have been made during the course of mouse typhoid infection of two serological types in mouse populations and of Friedländer and pneumococcus infection in mouse populations. A total of 300 or 400 tests have been made under many conditions to test the theory of fluctuating virulence. The results were invariably negative and showed a constancy and fixity of disease-producing power of a given strain of organisms under all conditions of natural infection.

Still another method has been used by both Topley and ourselves to compare virulence of bacterial strains, namely, that of introducing the test agent into herds of susceptible animals and noting its potency in spreading and inducing fatal disease. Topley states that theoretically virulence may be a very complicated series of factors and that disease-producing power, as measured by the natural inoculation of individual mice, may not measure disease-producing power as determined by the ability of organisms to cause disease in herds. We know of no experimental basis for assuming the operation of additional mysterious properties, nor can we conceive of any factor inherent in the agent which would operate in the herd and not in the individual. Nevertheless, we performed a number of tests on mouse typhoid, Friedlander, and *Pasteurella* organisms in mouse herds in the following manner. A culture was obtained from an animal in extremis at the height of an epidemic wave in an infected population, and others from stools or from nasal passages of healthy mice during inter-epidemic periods, when mortality was minimal. Each was administered to two or three mice by the normal portal of entry and these mice were in turn added to populations of healthy mice with no previous exposure to the infection. In each instance the infection spread throughout the herd and the curves of mortality among the mice exposed to the carrier or inter-epidemic cultures were the same as those among mice exposed to the epidemic strains. Once again we failed to note differences in epidemic or disease-producing capacity of organisms maintained and tested under normal conditions.

It is appropriate here to insert a statement concerning the changes in virulence which we have observed. That decreases in virulence of bacteria under the artificial conditions of laboratory culture may occur is a commonplace. It is, indeed, regarded as somewhat of a triumph when such deterioration is not encountered. We have induced avirulent variants of *Pasteurella* experimentally and in some instances have brought back the virulence of a strain to its original natural pathogenicity. We know of no instances except those reported by Griffith (10), in which a laboratory strain has been altered to possess a higher virulence than that which it enjoyed in Nature. Again we have tested strains of *Pasteurella* from different hosts and found them different in virulence. Some of them refused to become permanent parasites in the new mouse herds and after one or two epidemics failed to survive. Others were unable to become established in the first place. We conclude, therefore, that strains of organisms from different sources possess different amounts of herd virulence and that these amounts are stable. We also accept fully that under laboratory conditions virulence is depressed, or it may be enhanced to its original level, and, indeed,

altered qualitatively, as in the case of rabies virus. But that a given strain or a single unit in a given strain of organisms, when maintained under natural conditions, undergoes fluctuating or discontinuous alterations in disease-producing capacity is a theory not supported thus far by experimental facts.

Topley and his associates recently reached somewhat the same conclusion (11). While we define virulence as disease-producing power under natural conditions, he defines it as the potentiality to induce fatal infection under artificial or natural conditions. Topley calls infectivity the power of an organism to spread readily from one individual to another and induce in the hosts to whom it spreads a significant infection of any degree of severity. We know of no microscopic agent with an independent power to spread, but regard spreading as the intervention of some outside agency, such as man's spreading contaminated food to the dinner plate of the recipient, the spreading of yellow fever virus to the blood of a victim by mosquitoes, or the spreading of pneumococci to the nasal passages of a neighbor by man and subsequently air currents. Infectivity, then, apart from the ability of the agent to induce infection, once gaining access by an outside vehicle to the natural portal of entry of the susceptible host, remains a mystery to us.<sup>2</sup> Topley brings up the statistical approach by stating categorically the number of mice required to obtain a "significant" result. We should agree that his numbers may be accurate for the mice which he employs but that the number required is, in each circumstance, a function of the type of animal employed. He commences his description of experiments "by a reference to the only instance in which our observations have suggested that an epidemic wave of mouse typhoid has been initiated by the emergence of a virulent and infective variant from a relatively avirulent strain." His observations and inferences disregard the possibility that differences in the animals might affect his results and, since no mention is made of duplication or repetition of the chance differences in mortality, such happenings cannot be regarded as experimentally established. Indeed, Topley concludes this section as follows: "Finally we may note that, though we have never yet demonstrated a clear and indubitable variation in virulence or infectivity in *Bact. aertrycke* during an epidemic prevalence, we have never carried out a series of tests on a scale that would ensure the detection of such variants unless they constituted a high proportion of the total bacterial population. We should, however, agree with Webster that the evidence at present available suggests that *Bact. aertrycke* tends to retain a constant virulence under a variety of different conditions." Topley then proceeds to describe what he calls "a clear demonstration of an increase in the infectivity of *Past. muriseptica* during epidemic spread." He exposed mice to what appears to be a laboratory strain and took a culture from one of the few mice which died, and then exposed a second herd to this strain. This procedure was repeated until one strain so introduced infected and killed a majority of the population. This strain was then compared simultaneously with the agar stab cultures by inoculating twenty five mice intraperi-

<sup>2</sup> Finally and most important, we regard all these properties grouped under the head of virulence or pathogenicity to be as much an expression of host factors as of bacterial factors, unless proved otherwise. Experimental evidence for this statement will be given later.

toneally with each and placing them in contact with 100 normals. Few of the mice in contact with the laboratory strain died, whereas 60 per cent of those in contact with the herd strain died. Intraperitoneal virulence remained about the same. Now Topley did not repeat this procedure to determine whether the happening was a scientifically reproducible fact. Nor has he given us evidence that the happening was due to the agent rather than the mice. Later we shall demonstrate that precisely this event can be produced experimentally in two sets of mice with one culture and not, as Topley says "This series of tests demonstrates quite clearly that virulence and infectivity are not synonymous terms, and that the two characters must be studied and considered separately in any attempt to analyse the epidemic process from this angle." Topley's final conclusion on the subject of virulence is as follows: "Taking these observations as a whole, they seem to us to lend strong experimental support to the view that variations in the character of a bacterial parasite may well be of decisive importance in the secular history of any epidemic disease, and in the determination of the differences that have so often been noted in the behaviour of epidemics of the same disease occurring in different places during a relatively short period of time. We do not think that our evidence supports the view that a variation in the characters of the parasite is an essential, or even a frequent, concomitant of the evolution of a single epidemic wave, with its characteristic rise and fall. It is in the long-distance development of the epidemic process, or in the introduction or evolution of epidemic strains among particular herds, that this factor would seem to play its most significant part."

## PART 2 THE HOST FACTOR

From a consideration of the virulence factor and its effect in the field of experimental epidemiology, we turn now to the *host factor*. "What part does it play in the rise and fall of epidemics? What determines survivorship of an epidemic? An old and unsolved question among epidemiologists is whether an individual survives an epidemic because of the acquisition of a specific immunity through chance contact with small doses of the infectious agent or because of an initial inherent resistance."<sup>3</sup> Do "individuals actually differ in inherent resistance? Do they succumb to or escape an epidemic according to this initial resistance?"<sup>4</sup> "Because of the vast amount of indirect evidence pointing to differences and fluctuations in host susceptibility and their importance in determining the spread of infection, it is fundamentally important to epidemiology that this factor be quantitatively analyzed. This analysis *must* consist of an investigation of possible racial, individual, environmental, and acquired specific components."<sup>5</sup>

The problem of survivorship "was tested in experimental epidemics by Topley and Greenwood and by ourselves. Both found that the introduction of *B enteritidis* into a population of susceptible mice brought about an epidemic fatal

<sup>3</sup> Report of Dr. L. T. Webster to the Board of Scientific Directors, The Rockefeller Institute for Medical Research, April, 1938.

<sup>4</sup> Scientific Monthly, 1939, 48, 69.

<sup>5</sup> Old unpublished notes on Monograph.

to many but leaving survivors. Moreover, the addition of immigrants maintained the infection indefinitely but continued to spare certain individuals longer than others. Topley and Greenwood regarded these survivors as individuals immunized by small doses of *B. enteritidis*, we, on the other hand, considered the possibility that they might have been innately resistant at the outset. Accordingly Topley viewed the constituents of an uninfected population as alike with regard to their initial resistance, we, on the contrary, took the view that individuals might differ widely in their initial resistance. Obviously the question of survivorship could not be tested directly until not only the average resistance of a population at the outset but the resistance of each individual was known. In 1922 (12) therefore, we commenced selective breeding experiments to determine in the first place whether unexposed individuals were all alike in their resistance to infectious agents and, in the second place, whether lines of uniform susceptibility might be developed. Now, some 20 years later, we can state definitely that individuals do differ widely in their initial resistance to bacteria and viruses. Moreover, through strict selective inbreeding we have developed a line of mice with 95 per cent of the individuals highly susceptible to *B. enteritidis* and another line from similar parentage with 95 per cent of the individuals highly resistant."<sup>6</sup>

"The groundwork of experimental knowledge of the inheritance of resistance to infectious disease was laid by workers with plant diseases. Biffen, in 1905, cross-bred strains of wheat resistant to yellow rust with strains susceptible and by testing  $F_1$  and  $F_2$  progeny under field conditions, demonstrated its dependence upon a single factor type of inheritance with susceptibility dominant. His homozygous strains were not completely resistant or susceptible, respectively, but mainly of high or low resistance. He noted that modifications in amount of available nitrogen increased the susceptibility of genetically resistant individuals. Burkholder, in 1918, and McRostie, in 1919, studying the inheritance of resistance of beans to anthracnose, employed non infected greenhouse stock and controlled dosage by inoculating each individual in the greenhouse with a similar amount of the more pure strain of the infecting agent. Each found resistance inherited and based upon a single factor mechanism with resistance dominant. Many plant infections have now been studied with techniques aiming at once at naturalness of mode of infection consistent with adequate control. Results were compared with those of a field test. Resistance was found to be inherited in some instances on a multiple and in some on a single factor basis with resistance dominant (resistance of wheat to a) stem rust, b) leaf rust, c) bunt, resistance of d) barley to rusty blotch, e) cabbage to yellows, f) maize to rust, h) oats to loose smut) more frequently than susceptibility. Inborn resistance to one infection generally proved independent of resistance to another. No anatomical or physical mechanism has thus far been proved causally related to resistance or susceptibility.

"Workers on infectious diseases of animals have paid little attention until

<sup>6</sup> Report of Dr. L. T. Webster to the Board of Scientific Directors, The Rockefeller Institute for Medical Research, April, 1938.

recently to the possible regulation of resistance by inborn factors and to the differentiation of individuals according to these factors. Common practice showed that if a batch of animals was given an injection of a virulent agent by some artificial route, the great majority succumbed within a few hours. Again, if less virulent agents, smaller doses, or more natural routes of infection were used, a percentage of a random batch of individuals might survive, but if the test was run in duplicate or repeated, the percentage of survivors varied in a random manner. Greenwood and Topley had experience with this sort of result and attributed differences in survival rate and in the fate of individuals to uncontrolled errors of technique.

"An experimental attack on the question in fowl and rodents was undertaken by Frateur in 1924, Roberts and Card in 1926, Lambert and Knox in 1928, Irwin in 1929, Schott in 1932, and Gowen and Schott in 1933. All bred for resistance from survivors of a highly artificial infection and noted a progressively declining mortality. They crossed the selected survivors with either the original unselected stock or with a susceptible strain and tested  $F_1$ ,  $F_2$ , and backcross progeny. Frateur and Gowen and Schott interpreted their figures as suggesting a single factor type of Mendelian inheritance with resistance dominant, the remainder accounted for their data on a multiple factor basis. These workers employed materials and techniques, however, which rendered their results difficult of interpretation from an infectious disease point of view. In the first place, the test infection was suspected of persisting in their stock since survivors were used for breeding. The presence of the infection involved risks of dam and sire infecting each other and of a part of the litter dying from the infection, leaving survivors for later tests which might have proved resistant (a) because of their selection through previous infection or (b) because possessed of an active or (c) a passive immunity. Irwin and Gowen and Schott especially have endeavored to minimize the significance of a transfer of passive immunity in influencing their data, but the probability remains that the persistent infection was a factor in enhancing the resistance of their test progeny. In the second place, resistance has been tested to highly artificial infections,—intraperitoneal injections of large doses, bacteria of low natural infectivity,—without determining experimentally whether such tests were in fact a measure of the resistance of the individual to the infection in Nature. Indeed, experiment has often shown the contrary to be the case in that resistance of animals to bacterial infections differed according to the portal of entry employed, and animals susceptible by an artificial route were not necessarily as susceptible by a natural route, and *vice versa*. In the present state of knowledge, therefore, it is important for the worker to indicate clearly the type of resistance he is studying and determine in each instance the degree to which this resistance is a measure of resistance in Nature.

"Our investigations in inborn resistance commenced in 1922, when it was found that batches of animals bred in the laboratory in an effort to control all possible environmental variables, if exposed to infectious agents in a way simulating Nature, differed from batches of uncontrolled mice of the sort discussed by Greenwood and Topley in responding as a group in a relatively predictable manner.

Moreover, the survival of some individuals, as contrasted with the death of others under apparently similar and controlled conditions, took on a possible significance. Although the reaction of a given individual of the group could not be predicted, the differences in individual response were regarded as possibly due not to technical irregularities, but to differences in their degree of inborn resistance.

"This idea was supported by experiments showing that certain strains of mice suffered consistently higher mortalities than others following *per os* instillation of mouse typhoid bacilli and also following exposure to a naturally spreading herd infection. Selective breeding experiments showed that progeny of individuals surviving a *per os* instillation of mouse typhoid bacilli suffered less mortality, and progeny of individuals succumbing early to the infection suffered greater mortalities following the test infection than the unselected controls. In these tests, however, the original population was too small to insure the selection of individuals with the widest possible differences in inborn resistance characteristic of the strain, and was too small to insure that the selected lines would provide a sufficient number of fertile dams. Then too, the resistant lines were bred from survivors, and the bread and milk diet produced mice whose mortalities fluctuated with season. The findings, however, in spite of their limitations, pointed consistently toward the presence of innate differences in resistance. Consequently, the breeding experiments were repeated with an original population of 600 to cover the susceptibility range of the strain and allow for selection of optimum breeders with progeny exhibiting the desired maximum and minimum mortalities. Moreover, a diet was used which gave relatively stable mortality percentages in unselected controls. Here, although an error was committed in making the first selection for resistants from survivors rather than from the unexposed progeny of mice which were later proved survivors, these selected survivors were proved free of infection before being introduced into the colony, and thereafter selections were made from unexposed sibling litters."

*Technique of Selective Breeding Experiments*—The selective breeding of Rockefeller Institute mice was carried out in the following manner. 500 females were mated at random with 100 males. The young were weaned at 4 weeks. At this time the parents were given the standard dose of *B. enteritidis*. In instances in which both parents died within 10 days after infection, the progeny were reserved as the susceptible stock. Subsequent matings were made, brother to sister. In instances in which both parents survived the infection, the progeny were injected. If all progeny survived, the surviving parents were tested twelve times for the presence of *B. enteritidis* in their stools. Those persistently negative were mated again. In instances in which two tested litters survived, a third litter was obtained and reserved as the resistant stock. Matings were then made brother to sister. Subsequently, the established breeding stock and all progeny have consisted of animals never exposed to infection. Further selections have been made entirely on the basis of the progeny test, that is, of per cent mortality of two lit-

ters and fertility of sire and dam. In the case of the susceptible lines, animals were discarded if two litters showed a mortality less than 80 per cent, and in the case of the resistant lines, a mortality greater than 20 per cent. The tests were made at the first of each month. At the same time 50 unselected mice, raised under identical conditions, were likewise tested as controls. The same mouse strain of *B. enteritidis* has been employed throughout, observed carefully, and kept under uniform conditions at ice box temperature. In so far as can be determined, the strain has not altered.

"It is important to restate that the colony of about 3,500 mice was continually tested for the presence of mouse typhoid and other intercurrent infections. The progeny of susceptible, resistant, and other lines were housed together at random, six to eight per cage, after weaning for at least 4 weeks, and no infection took place. Many samples of normal mice were sacrificed and cultured at autopsy. Carrier tests on all breeding stock were made as routine. The death rate of mice more than 1 week old was less than 0.1 per cent per month. All mice found dead were autopsied and cultured. The stock apparently remained free of infection.

*"Maintenance of Unselected Control Mice*—Housed with selected mice and kept under identical conditions were the breeding stock and litters of the unselected Rockefeller Institute mice. Some were bred brother to sister, some were pen inbred.

"Text-Fig. 6 shows the crude data of per cent mortality of twenty-six tests on a total of 771 unselected, 2,942 selected susceptible, and 2,265 selected resistant Rockefeller Institute mice. In each test the sets of mice, brought up under identical conditions and of the same age, received the stated dilution of the same culture. Prior to August, 1931, all received the same dose, later the susceptible batches received a smaller and the resistant a larger dose than the unselected batches. The only known variable which could account for the differences in mortality was heredity."<sup>8</sup>

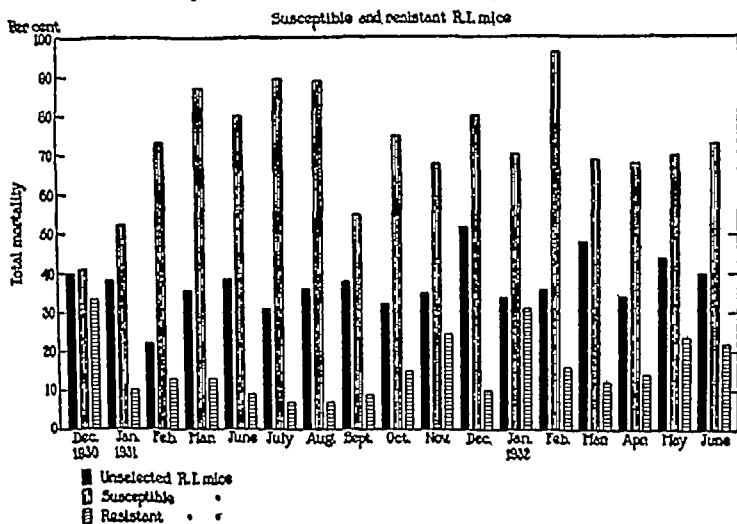
"Later experiments in their entirety demonstrated that the individual constituents of any sizable population of mice in which environmental variables have been controlled as far as possible differed widely in their innate resistance to infectious agents. This difference was of the order of 1,000 lethal doses or of mortalities to a standard dose of 95 per cent as contrasted with 15 per cent. These innate differences in the resistance of individual mice were brought out by the progeny test and by the development of lines from certain individuals by selective breeding. This procedure segregated at the outset individuals whose resistance was maximum or minimum, respectively, remaining unchanged for twelve generations. The resistance of the majority, however, was intermediate, increasing or decreasing on repeated selection from generation to generation. Crossing the initially highly susceptible and resistant lines and testing  $F_1$ ,  $F_2$ , and backcross progeny resulted in percentage mortalities in the neighborhood of those expected on the basis of a single factor type of Mendelian inheritance for resistance to *B. enteritidis* and to encephalitis virus. Resistance proved dominant in

<sup>8</sup> J. Exp. Med., 1933, 57, 795



each instance. Moreover, the histories of the direct descendants in each line (Tables III to V) supported the theory of a single factor type of inheritance, since mortalities in succeeding generations showed mainly no definite progress with selection but proved relatively stable. Consequently, we regarded the above as evidence of a single main factor type of inheritance with possibly a number of small modifiers.

"Individuals inherently resistant or susceptible to one infectious or toxic agent may or may not prove likewise resistant or susceptible to another. Previously we noted that survivors of mouse typhoid or individuals fed on McCollum ration were relatively resistant not only to a subsequent injection of an anti-



TEXT FIG. 6. COMPARATIVE MORTALITIES OF UNSELECTED AND SELECTED R. I. MICE FOLLOWING INTRASTOMACHAL INSTILLATION OF *B. ENTERITIDIS* MOUSE TYPHOID BACILLI

genically different strain of mouse typhoid but to mercuric chloride. This indicated to us that resistance was conditioned not only by specific immunity but by non-specific factors as well. The association of resistance to mouse typhoid and to mercuric chloride was considered not as necessary nor as an indication of a panresistance, as Hill has inferred. Rather the parallel was one of chance. This supposition was borne out by studies in which from hybrid stock, lines were segregated with various combinations of resistance and susceptibility, namely, the BSVS line, susceptible to two enteric and three respiratory tract bacterial and three virus infections, BRVR line, resistant to all save rabies, BSVR line, susceptible to the bacterial and resistant to two of the three tested virus infections, and the BRVS line, resistant to the bacterial and susceptible to the virus

infections And finally, the cross-breeding of these strains and testing of progeny brought out the independence of genetic factors governing resistance to *B enteritidis* and encephalitis virus, respectively It followed that the amount of in-

TABLE III

*Immediate Family Histories of Inbred BSVS Lines with Respect to Mortalities Following Test Injections of B enteritidis or Virus*

LINE BACTERIA-SUSCEPTIBLE-VIRUS-SUSCEPTIBLE A (BSVS)							LINE BACTERIA-SUSCEPTIBLE-VIRUS-SUSCEPTIBLE B (BSVS)					
Generation	Progeny tested with <i>B enteritidis</i>			Progeny tested with virus			Progeny tested with <i>B enteritidis</i>			Progeny tested with virus		
	No injected	No dead	Per cent dead	No injected	No dead	Per cent dead	No injected	No dead	Per cent dead	No injected	No dead	Per cent dead
1	17	14	82 4									
2	44	36	81 8									
3	91	87	95 6									
4	26	24	92 3									
5	27	27	100				18	18	100			
6	11	11	100	12	8	66 7	20	19	95	23	16	69 6
7				24	21	87 5				34	25	73 5
8				23	23	100				37	35	94 6
9	3	3	100	207	183	88 4	8	8	100	144	128	88 9
10	37	37	100	192	168	87 5	11	11	100	155	121	78 1
11	13	13	100	32	27	84 4	16	16	100	24	23	95 8
12	23	23	100	26	25	96 2	12	12	100	13	13	100
Totals	292	275	94 2	516	455	88 2	85	84	98 8	430	361	84 0

TABLE IV

*Immediate Family Histories of Inbred BSVR Lines with Respect to Mortalities Following Test Injections of B enteritidis or Virus*

LINE BACTERIA-SUSCEPTIBLE-VIRUS-RESISTANT (BSVR)						
Generation	Progeny tested with <i>B enteritidis</i>			Progeny tested with virus		
	No injected	No dead	Per cent dead	No injected	No dead	Per cent dead
4	9	9	100			
5	15	15	100			
6	21	21	100	59	1	1 7
7				42	1	2 4
8				33	3	9 1
9	15	14	93 3	70	6	8 6
10	9	8	88 9	19	1	5 3
11	37	35	94 6	46	6	13 0
Totals	106	102	96 2	269	18	6 7

herent resistance displayed by an individual to an infectious agent cannot be taken without experiment as a measure of its resistance to another

"The effect of unforeseen environmental variables on the manifestation of

genetic factors was disturbing in carrying out this sort of experiment. Control measures were frequently inadequate to prevent variations in results such as the sudden increase of 15 to 20 per cent in mortality percentages in all lines recorded in the present experiments. The expression of genetic factors was conditioned by the expression of somatic factors and the experiments could achieve at best but a measure of the summation effect of both under conditions in which the environmental ones have been controlled as far as possible.

"In concluding this analysis, we point out again the close parallelism between our findings and those of workers on plant diseases.

"The thesis of variability of host resistance and its regulation by inborn and environmental factors has both particular and general bearing upon experimentation in infectious disease. The particular effect of innate factors on type of clinical disease and tissue changes was exemplified in studies on susceptible and

TABLE V  
*Immediate Family Histories of Inbred BRVS Line with Respect to Mortalities Following Test Injections of B. enteritidis or Virus*

Generation	Progeny tested with <i>B. enteritidis</i>			Progeny tested with virus		
	No. injected	No. dead	Per cent dead	No. injected	No. dead	Per cent dead
1	4	0	0			
2	16	0	0			
3	22	0	0			
4	82	14	17.1			
5	29	5	17.2	20	19	95
6	43	15	34.9	30	38	97.4
Totals	196	34	17.3	59	57	96.6

resistant mice following oral administration of *B. enteritidis*, and nasal administration of pneumococci and encephalitis virus.

"In general, the concept of control of host variables enforces a conservative attitude in judging seemingly contradictory results of different workers unless their test animals are comparable in all respects. And finally, standardized animals, like pure reagents in chemistry, should provide a means of elucidating many of the quantitative problems in infectious disease."

"Thus our assumption became established that individuals differ profoundly in their inherent resistance to a given infection"<sup>10</sup> according to the following conclusions from our work published in 1937:

"Under the conditions described in this paper, there may be selected promptly from a hybrid stock of mice, of which 40 to 50 per cent die following a standard dose of *B. enteritidis* or St. Louis encephalitis virus, lines in which as high as 95 per cent and as low as 15 per cent succumb. Three lines,—one bacteria-suscep-

<sup>10</sup> J. Exp. Med., 1937, 65, 282.

<sup>11</sup> Scientific Monthly, 1939, 48, p. 70, under (A).

infections And finally, the cross-breeding of these strains and testing of progeny brought out the independence of genetic factors governing resistance to *B enteritidis* and encephalitis virus, respectively It followed that the amount of in-

TABLE III  
*Immediate Family Histories of Inbred BSVS Lines with Respect to Mortalities  
Following Test Injections of B enteritidis or Virus*

LINE BACTERIA-SUSCEPTIBLE-VIRUS-SUSCEPTIBLE A (BSVS)							LINE BACTERIA-SUSCEPTIBLE-VIRUS-SUSCEPTIBLE B (BSVS)					
Generation	Progeny tested with <i>B enteritidis</i>			Progeny tested with virus			Progeny tested with <i>B enteritidis</i>			Progeny tested with virus		
	No injected	No dead	Per cent dead	No injected	No dead	Per cent dead	No injected	No dead	Per cent dead	No injected	No dead	Per cent dead
1	17	14	82.4									
2	44	36	81.8									
3	91	87	95.6									
4	26	24	92.3									
5	27	27	100				18	18	100			
6	11	11	100	12	8	66.7	20	19	95	23	16	69.6
7				24	21	87.5				34	25	73.5
8				23	23	100				37	35	94.6
9	3	3	100	207	183	88.4	8	8	100	144	128	88.9
10	37	37	100	192	168	87.5	11	11	100	155	121	78.1
11	13	13	100	32	27	84.4	16	16	100	24	23	95.8
12	23	23	100	26	25	96.2	12	12	100	13	13	100
Totals	292	275	94.2	516	455	88.2	85	84	98.8	430	361	84.0

TABLE IV  
*Immediate Family Histories of Inbred BSVR Lines with Respect to Mortalities  
Following Test Injections of B enteritidis or Virus*

LINE BACTERIA SUSCEPTIBLE-VIRUS-RESISTANT (BSVR)						
Generation	Progeny tested with <i>B enteritidis</i>			Progeny tested with virus		
	No injected	No dead	Per cent dead	No injected	No dead	Per cent dead
4	9	9	100			
5	15	15	100			
6	21	21	100	59	1	1.7
7				42	1	2.4
8				33	3	9.1
9	15	14	93.3	70	6	8.6
10	9	8	88.9	19	1	5.3
11	37	35	94.6	46	6	13.0
Totals	106	102	96.2	269	18	6.7

herent resistance displayed by an individual to an infectious agent cannot be taken without experiment as a measure of its resistance to another

"The effect of unforeseen environmental variables on the manifestation of

genetic factors was disturbing in carrying out this sort of experiment. Control measures were frequently inadequate to prevent variations in results such as the sudden increase of 15 to 20 per cent in mortality percentages in all lines recorded in the present experiments. The expression of genetic factors was conditioned by the expression of somatic factors and the experiments could achieve at best but a measure of the summation effect of both under conditions in which the environmental ones have been controlled as far as possible.

"In concluding this analysis, we point out again the close parallelism between our findings and those of workers on plant diseases.

"The thesis of variability of host resistance and its regulation by inborn and environmental factors has both particular and general bearing upon experimentation in infectious disease. The particular effect of innate factors on type of clinical disease and tissue changes was exemplified in studies on susceptible and

TABLE V  
*Immediate Family Histories of Inbred BRVS Line with Respect to Mortalities  
Following Test Injections of B enteritidis or Virus*

Generation	Progeny tested with <i>B. enteritidis</i>			Progeny tested with virus		
	No. injected	No. dead	Per cent dead	No. injected	No. dead	Per cent dead
1	4	0	0			
2	16	0	0			
3	22	0	0			
4	82	14	17.1			
5	29	5	17.2	20	10	95
6	43	15	34.9	30	38	97.4
Totals	196	34	17.3	50	57	96.6

resistant mice following oral administration of *B. enteritidis*, and nasal administration of pneumococci and encephalitis virus.

"In general, the concept of control of host variables enforces a conservative attitude in judging seemingly contradictory results of different workers unless their test animals are comparable in all respects. And finally, standardized animals, like pure reagents in chemistry, should provide a means of elucidating many of the quantitative problems in infectious disease."

"Thus our assumption became established that individuals differ profoundly in their inherent resistance to a given infection"<sup>10</sup> according to the following conclusions from our work published in 1937.

"Under the conditions described in this paper, there may be selected promptly from a hybrid stock of mice, of which 40 to 50 per cent die following a standard dose of *B. enteritidis* or St. Louis encephalitis virus, lines in which as high as 95 per cent and as low as 15 per cent succumb. Three lines,—one bacteria suscep-

<sup>9</sup> J. Exp. Med., 1937, 65: 282.

<sup>10</sup> Scientific Monthly, 1939, 48: p. 70, under (A).

table-virus-susceptible, one bacteria-susceptible-virus-resistant, and one bacteria-resistant-virus susceptible,—were regarded as remaining relatively stable after approximately twelve generations of selection and brother to sister or line inbreeding

"Crossing susceptible with resistant lines and testing  $F_1$ ,  $F_2$ ,  $F_3$ , and backcross progeny resulted in mortality percentages in the neighborhood of those expected on the basis that resistance to *B enteritidis* and to encephalitis virus was each inherited independently on a single factor basis with resistance dominant over susceptibility

"A bacteria-resistant-virus-resistant line has been developed from a cross between bacteria-susceptible-virus-resistant and bacteria-resistant-virus-susceptible lines

"All selected lines proved uniformly susceptible to a strain of mouse passage rabies virus"<sup>11</sup>

"To test whether certain epidemics were due to fluctuations in population resistance and whether those individuals who escaped were those most resistant at the outset, populations had to be made up of individuals whose resistance was known. This had not been possible until pure-bred lines of mice of known and uniform resistance were developed. From the progeny of resistants and susceptibles described above, continued inbreeding and selection have been practised for fifteen generations until now lines of mice are at hand generally indistinguishable except that one is 10,000 times more susceptible to a given infectious agent than the other"<sup>12</sup> "Therefore, by using these mice whose individual susceptibilities, both innate and environmental, were known and controlled, direct experimental data have been obtained for the first time on the problem of survivorship

"These mice were combined in various proportions to make up populations into which mouse typhoid was introduced. A single cage of standard size was used for simplicity, although a crowding factor exerted a definite influence on mortality. Mouse typhoid was introduced by feeding *B enteritidis* by stomach tube to certain individuals and subsequently adding them to the population and permitting the resulting infection to spread among the constituents 'naturally'. Cages were cleaned as routine. The modified Steenbock diet was employed. Dead mice were autopsied and cultures taken of spleen for identification. The first problem undertaken was a study of the epidemiology of mouse typhoid in a population in which at least 50 per cent of the mice were known to be inherently resistant. A typical experiment is described in detail

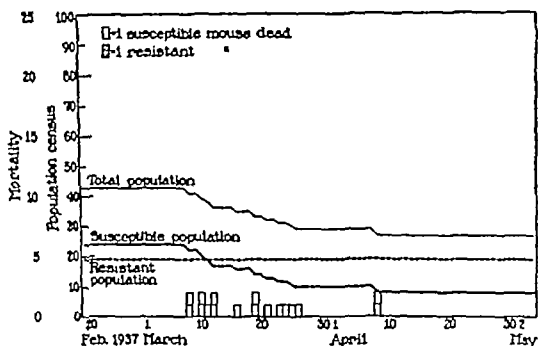
"Twenty-four Swiss mice with identifying marks were placed in a pen with nineteen mice of the selected resistant strain likewise marked

"Ten mice of the selected susceptible line were marked and each given by stomach tube 0.5 cc of broth containing 5,000,000 *B enteritidis* mouse typhoid organisms. Twenty-four hours later they were added to the above population. The experimentally infected mice commenced dying on the 6th, and were all dead

<sup>11</sup> J Exp Med, 1937, 65, 285

<sup>12</sup> Scientific Monthly, 1939, 48, p 70, under (B)

of mouse typhoid by the 9th day. The Swiss contacts commenced dying on the 18th day and continued thereafter for 32 days (Text-Fig 7). During this period sixteen Swiss mice (66 per cent) died, of which thirteen were autopsied and proved positive for mouse typhoid bacilli. This 66 per cent mortality was in accord with the prediction based on *per os* titrations. We had, of course, no prior knowledge as to which Swiss individuals would succumb and therefore did not know whether the 34 per cent which survived were at the outset inherently resistant or had acquired an immunity through non fatal infection and had therefore survived. Twenty-six days following the last fatality the eight Swiss survivors were sacrificed and autopsied. Five (62 per cent) showed positive spleen cultures and one serum agglutinins titering 1 to 10. The striking result of this test was that according to prediction none of the inherently resistant mice succumbed. At autopsy, however, following completion of the experiment, eight (58 per cent) had positive spleens. The relative proportion of susceptibles and resistants in-



TEXT FIG 7 FATE OF SUSCEPTIBLE AND RESISTANT MICE EXPOSED TO *B. ENTERITIDIS* MOUSE TYPHOID

ected was similar, although mortalities were widely different. This relationship has been pointed out before as indicating plainly that so-called infectivity versus virulence phenomena cannot be regarded as distinctive properties of the parasite (Greenwood, Hill, Topley and Wilson, 1936) but can be shown by epidemiological experiment to be phenomena dependent upon host differences.

"The next problem was to test further the selective mortality among the susceptibles and to discover whether any susceptibles could become immunized through exposure. Each of four populations, A, B, C, and D, was made up by combining in a single pen twenty susceptibles with twenty resistants, all identified, of these four, the course of the epidemic in population A only is now described in detail.

"Ten white-faced mice, each of which had received the standard dose of mouse typhoid bacilli the previous day, were added, the same routine was then carried out as described in the previous experiment and observations were continued for

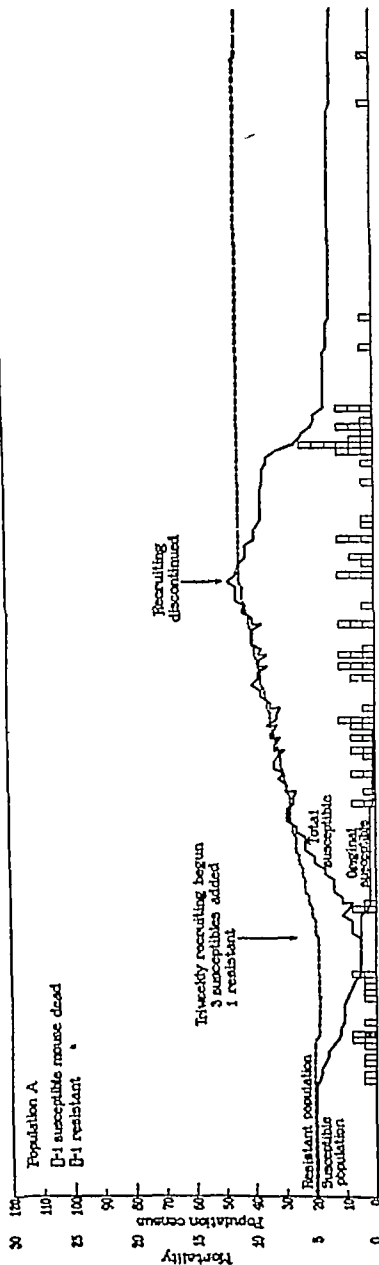
44 days. The results are shown in Text-Fig 8 (Population A) 80 per cent of the white-faced carriers introduced into the pen died of mouse typhoid. Mortality among the susceptible contacts totalled 75 per cent. In contrast, only one of thirty resistant contacts succumbed. This difference showed clearly that in such a population mortality was confined almost exclusively to those contacts known at the outset to be inherently susceptible. The effect of immigration upon selective mortality among both original constituents and the recent recruits was then tested, 44 days after the population was first infected, by adding three susceptibles plus one resistant three times a week. Recruiting was discontinued 2 months later, observations were made for a total of 5 months after recruiting had been commenced. The results are shown in Text-Fig 8. The census following triweekly recruiting of three susceptibles plus one resistant increased relatively steadily until a maximum of 92 was reached. At this point an equilibrium seemed to be established between number of recruits and amount of mortality. Following the cessation of recruiting, however, mortality still continued at a high rate for about 1 month, reducing the census by more than 50 per cent, subsequently few deaths occurred for the last 2 months. Throughout the 5 months' period, mortality was limited almost exclusively to the innately susceptible mice and these all died of mouse typhoid. The remaining original susceptibles succumbed within  $2\frac{1}{2}$  months, thus failing to show any evidence that they had been immunized through exposure. 83 per cent of recruits succumbed within 5 months, probably all of mouse typhoid. In contrast, practically all resistants, both original constituents and later recruits, remained well, one died but not of mouse typhoid."<sup>13</sup>

Hence "fluctuations in infectivity and virulence in infected mouse populations as investigated thus far proved to be manifestations of differences in host resistance rather than in parasite potentialities. A single strain of mouse typhoid bacilli spread equally to resistant and to susceptible mice but showed at the same time a high killing potency in susceptibles and a low killing potency in resistants. Altering resistance through diet altered killing potency but not infectivity. On the other hand, when host resistance factors were kept constant and uniform through the use of mice of known susceptibility, infectivity and virulence likewise remained constant.

"Mortality from mouse typhoid in exposed or infected populations was conditioned by the number of highly susceptible constituents. If the number was few, deaths were sporadic, if great, epidemic, if susceptibles were depleted, mortality subsided. Previously it was known that fresh mice added to an infected population initiated or maintained mortality at epidemic levels, but their exact rôle had remained uncertain. Topley and Greenwood who considered the fresh mice to be alike in their individual susceptibilities furnished no experimental data as to their function. We found that the fresh mice differed in their initial susceptibilities but were in doubt as to whether these individual differences or the average level of susceptibility was the more important. It now appeared that the presence of the individual with high susceptibility initiated the outbreak, no matter what the

<sup>13</sup> J. Exp. Med., 1939, 70, 193





TEXT FIG 8 FATE OF SUSCEPTIBLE AND RESISTANT MICE EXPOSED TO B ENTERITIDIS MOUSE TYPHOID

general level of susceptibility might be. If these individuals were few in number, mortality remained sporadic, if numerous, it became and remained epidemic. Finally, if and when the susceptibles were depleted, mortality subsided. Thus the danger to an already infected population resides not alone in a general fall of the resistance level but in an immigration of highly susceptible individuals.

"A proportion of survivors were infected and remained the reservoir from which the infectious agent spread to incoming susceptibles.

"Clearly from these experiments, survivors were the initially resistant constituents and there was little or no tendency for susceptibles to become immunized through exposure to chance small doses.

"Reinoculation of survivors, as ordinarily practiced, is not a test of active immunity. Armstrong, for example, reported that since mice surviving nasal instillation of St. Louis virus were relatively resistant to a second instillation, they had been immunized. Such a conclusion was unwarranted without knowledge of whether some animals were resistant at the outset or whether all were susceptible. We have been unable to immunize known susceptible mice by instilling nasally sublethal doses of St. Louis encephalitis virus. In our opinion a test for active immunity must be made on batches of animals known to be at least 90 per cent susceptible to the test agent given by a normal portal of entry.

"Continued resistance of survivors did not depend necessarily upon the presence of bacilli in the tissues. If initial resistance was high, bacilli persisted indefinitely in the spleen without harm and without altering the already adequate level of resistance.

"In the foregoing experiments we were mindful that the resistance actually displayed by the individual was a summation of inherent components which were altered experimentally, plus environmental ones associated with age, regimen, and diet which were kept constant. Moreover, we knew by experiments under similar herd conditions that diet exerted equally important effects in epidemics under conditions in which inherited components were kept constant. The main point, after all, is that inherited and general environmental components of resistance are of fundamental importance, whereas immunological components associated with infection are of negligible importance in mouse typhoid infection.

"Therefore, to summarize. Under conditions in which mouse typhoid was allowed to spread naturally among herds of mice comprised of different proportions of individuals of innately high or low susceptibility: (a) 85 to 95 per cent of the innately susceptible succumbed to mouse typhoid in contrast to less than 5 per cent of the innately resistant, regardless of whether either constituted 25, 50, or 75 per cent of the population respectively. (b) The surviving population was therefore comprised largely of individuals known at the outset to be innately resistant. These resistants were, nevertheless, apt to have become infected and to harbor mouse typhoid bacilli in their spleens and feces. Under conditions in which recruits were added to surviving populations comprised chiefly of innately resistants among which mortalities had practically ceased: (a) Mouse typhoid infection spread to both innately resistant and susceptible recruits. (b) Mortality from mouse typhoid was limited almost exclusively to the innately suscep-

tible recruits and was 'sporadic' or 'epidemic' in character according to the numbers and proportion of susceptibles added (c) Innately resistant recruits remained well unless subjected to some non specific hazard, such as heat or overcrowding, in which case both they and the susceptibles succumbed in proportions similar to their relative numbers in the population. It was plain that survivors in both closed and open type epidemics were almost exclusively the individuals known at the outset to have been innately resistant. There was no tendency for known susceptibles to become immunized through herd exposure at epidemic times, at post-epidemic times in which the dosage of mouse typhoid bacilli was relatively small, nor at repeated short intervals."<sup>14</sup>

Thus, from the results of this work and the inferences and conclusions to be drawn from it, the *host factor* in experimental epidemiology assumes fundamental importance.

The application of "an experimentally developed theory of epidemics to human epidemiology involves certain difficulties. First, it is hazardous to reason by analogy from artificial experiments to field observations, where so many unknown and perhaps uncontrolled variables are involved. The experimental theory, however, rests upon data gained from a controlled study of six native animal infections observed under conditions as closely approximating Nature as possible. Again, the facts of human epidemiology have been gleaned under circumstances in which many variables operate and relatively few are controlled—hence they are subject to a limited interpretation. The present discussion is confined, therefore, to those human infections whose nature and specific agent are fairly well recognized.

"First of all, there are human infections whose prevalence fluctuates but little during a given year. These, of which tuberculosis is an example, are associated with causative agents whose virulence under natural conditions apparently remains stable. Their relatively high incidence in winter and their selective incidence appear to be due to differences in the seasonal resistances of populations and to individual differences in resistance.

"The fluctuating or epidemic infections of man may be divided crudely into those which are blood borne, food borne, or air borne. Those which are blood-borne—yellow fever and malaria, for example—usually arise from infected human beings or animals whose blood has contaminated some insect vector following bite. This insect vector in turn pierces the skin of man and introduces the infectious agent into his blood stream. The prevalence of these infections fluctuates markedly and epidemics occur of world wide proportions. The infections occur chiefly in warm weather and curves of incidence parallel those of prevalence of the insect vector and of temperature and humidity. That is to say, warm weather determines the number of insects, and the number of insects determines the available dosage of the infectious agent and consequently the number of human cases. The selective incidence among individuals depends upon differences in their resistance following exposure.

"The food borne infections of man—typhoid and dysentery, for example—

<sup>14</sup> J Exp Med, 1939, 70, 205

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<sup>14</sup> J Exp Med, 1939, 70, 205

arise from the ingestion of food, water, milk, etc , to which the causative organism harbored by man has gained access and multiplied. These diseases are most prevalent and become epidemic in tropical climates and in warm weather. Under these circumstances the causative agent is best able to multiply in contaminated material. The increase in quantity of the agent or dosage available to the population is the immediate cause of the epidemic.

"Finally, there is the group of air-borne infections—pneumococcus pneumonia, meningococcus meningitis, for example—which are transmitted directly from man to man by contaminated nasopharyngeal secretions without the intervention of any further vector. They are most prevalent in cold climates and cold weather and there may assume epidemic proportions. Some condition acting directly upon man increases carrier rates and hence dosage of disease-producing organisms available to the general population. Most probably these unknown winter conditions reduce the resistance of the general population, since deaths from all causes are most numerous at this time. And differences in individual resistance again appear to determine the selective incidence of the infection.

"Altogether the experimentally developed theory of epidemics fits the facts of human epidemiology better than the hypothesis of fluctuating virulence. Indeed, perhaps a crucial test has been the successful combating of the blood- and food-borne infections through a direct attack upon the dosage factor, that is, the control of insects and food and water contamination.

"If the fate of an individual during epidemic times depends not upon blind chance but upon this initial resistance, efforts to analyze and increase that resistance are of fundamental importance to preventive medicine. Thus far it appears that the basic inherent resistance of an animal to a given infection is not so much manifest at the portal of entry or blood stream as in the specific tissues to which the agent has a special predilection. Thus, in St. Louis encephalitis infection of mice, the nasal portal of entry of resistants or susceptibles is equally receptive and the blood stream of both contains no antibodies. But once the virus reaches its tissue of choice, the brain in this case, it multiplies rapidly in and destroys the brain of the susceptible, while in the brain of the innately resistant it gains a transitory foothold and causes little or no damage. Finally, studies now under way indicate that the level of resistance which is inherited can be altered by many environmental factors, entirely aside from specific vaccines or sera. Not the least of these factors, for example, is diet. Toward a better controlling and enhancing of the resistance levels of populations and of individual man studies are now directed."<sup>15</sup>

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DAVID LINN EDSALL

1869-1945

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1869-1945

This journal was started twenty-four years ago by Dr Howland and Dr Edsall. All too soon after its launching it was Edsall's sorrowful duty to write an appreciation of John Howland in June 1926. It is now our turn to write of David Linn Edsall who died on August 12, 1945.

The first impression that Edsall made on one was that he was a big man. Big in build, large in outlook and broad in grasp of any subject onto which he turned his interest. Standing six feet three with a massive head and kindly mien he was ever a striking figure. He used to say that in his early years in pediatrics, some children were afraid of him, they mistook him for a giant. And the years of his greatest medical activity, 1900 to 1930, had need of giants, for this was the period in which Medicine in America threw off provincialism and the proprietary schools and came to its maturity. From his first professorship at Pennsylvania through his professorship and deanship at Harvard he energetically and wisely pushed his plans for the improvement of medical teaching and the promotion of clinical research. His early training in the laboratory gave him an appreciation of what chemistry might do for medicine and kept him keen to study man in relation to his living environment, be it the fluid milieu of man's interior or the industry in which man labored. His work in Europe and various cities in America gave him a broad acquaintance with the leaders in medical teaching, and he was always making friends with the young men, giving to them freely of his wisdom and keeping himself young in point of view. All this made him a great Dean at the Harvard Medical School. Through his membership in many societies and committees, especially the Board of Trustees of the Rockefeller Foundation, he had a great influence on the development of medicine in America. During his twenty three active years in Boston he first reorganized and greatly developed the medical service at the Massachusetts General Hospital and then as full time Dean of the Harvard Medical School, from 1923 to 1935, he enriched that school by bringing in money to work with, by new concepts of full time teaching, and most of all by good appointments. He was ever on the lookout for men, and having met them enjoyed them, drew them out and remembered them later when positions were open at his own school or elsewhere. To use Howard Means' phrase, he was a "statesman in medicine" in the crucial years of its great development in America.

His friends will remember him as the kindly, philosophical companion of long tramps in the country. He loved the hills of New England and of the Carolinas. A walk with him brought out the silent enjoyment of exercise, trees and sky, interspaced with good talk of problems of mutual interest, a comfortable smoke and many good stories about folks, humble, medical and academic.

Those were great days and he was a great figure in them. We shall not see his like again.

STANLEY COBB



# THE OCULAR CHANGES OF PRIMARY DIFFUSE TOXIC GOITRE

## A REVIEW

ALAN C WOODS, M.D

*From The Wilmer Ophthalmological Institute of The Johns Hopkins Hospital and University*

The various ocular changes of hyperthyroidism occur predominately in primary toxic goitre. Ocular changes do not occur in colloid goitre. In simple adenomatous goitre and secondary toxic adenoma, ocular changes are rare and when they do occur are limited as a rule to minor lid and external signs. Exophthalmos either rarely or never occurs in secondary toxic goitre. In fact, the occurrence of a real exophthalmos in a supposed secondary toxic goitre at once introduces the question of the validity of the diagnosis and the probability of the condition being a primary diffuse toxic goitre.

The ocular changes in primary diffuse toxic goitre may be divided into four general groups, which may be present either individually or in combination. These four groups, and the important signs in each group, are <sup>1</sup>

1 Lid signs. These are the signs of Dalrymple, von Graefe, Stellwag, Joffroy, Gifford and Rosenbach. 2 External changes in the lids or eye. Excessive lacrimation and Jellinek's, Loewi's and Moebius' signs. 3 Extra-ocular palsies and ptoses. 4 Exophthalmos.

The various statistical studies on the incidence of ocular changes in different types of goitre (1, 2, 3, 4, 5), indicate the lid signs may occur either in simple adenoma, in secondary toxic adenoma, or in primary toxic goitre, being definitely more frequent in primary toxic goitre. The external changes, excessive lacrimation, Jellinek's, Loewi's and Moebius' signs are less frequent than the lid signs. They may be present either in secondary or primary toxic goitre, being more frequent in the latter. Extra-ocular palsies and ptoses are rare complications and occur almost exclusively in true primary toxic, or exophthalmic goitre. Exophthalmos occurs almost exclusively in primary toxic goitre. If present in secondary toxic adenoma it is always of low degree, less than 16 mm.

### LID SIGNS OF HYPERTHYROIDISM

*Dalrymple's sign.* This classical sign is widening of the lid slit on fixation. It is due to a retraction of the upper lid, with resultant enlargement of the lid slit and exposure of a rim of sclera above the upper limbus. It therefore gives the impression of exophthalmos, although it may occur without any actual protrusion of the eye.

<sup>1</sup> A number of other vague ocular changes have been described as occasionally present in primary toxic goitre. The relationship of these various ocular changes lagophthalmos, mydriasis, pupillary inequality, nystagmus, abnormal pulsation of retinal arteries, pigmentation of conjunctivae, bruise over eyeballs, etc. to primary toxic goitre have not been established and it is doubtful if they are other than coincidental changes. They will not be considered in this discussion.

This ocular change in hyperthyroidism was recognized as early as 1849, when White Cooper (6) described in primary toxic goitre a widening of the lid slit together with an apparent protrusion of the eye. He gave the explanation of his friend Dalrymple for the phenomenon. He stated that Dalrymple had seen several such cases and believed it was due to an "absence of proper tonicity of the muscles by which the eyes are retained in their natural position in the orbit and to some degree of venous congestion of the tissues forming the cushion behind the globes." This earlier description apparently confused the widening of the lid slit with a true exophthalmos. However, Dalrymple's name became irrevocably associated with the sign despite this confusion and this erroneous explanation, and today the retraction of the upper lid and widening of the lid slit on fixation is universally known as Dalrymple's sign.

The retraction of the upper lid does not interfere with the closure of the lids, although the lower lid appears to cover a little more of the cornea than normally. When the lids are closed there is a rather characteristic fold in the skin above the tarsus of the upper lid (7).

Holloway reported that in his series the Dalrymple sign was present in 46 per cent of the patients with primary toxic goitre, in 9 per cent of patients with secondary toxic goitre, and in 18 per cent of patients with simple goitre.

*Von Graefe's sign* The original description of lid lag by von Graefe in 1864 (8) leaves little or nothing to be added. He described accurately the disturbance of synergistic movements between the upper lid and elevation and depression of the globe. He noted that in healthy people if the globe were elevated or depressed, the upper lid made a corresponding motion, while in patients with primary toxic goitre the depression of the eye was not followed by the usual smooth closure of the upper lid, the lid either lagging behind the eye, or failing to close as the eye was depressed.

Von Graefe emphasized that this sign was entirely independent of exophthalmos, that it might be one of the earliest signs of hyperthyroidism, that if exophthalmos later developed the lid lag might disappear, and that the symptoms might vanish when the patient was under the influence of morphine or other drugs that affected nerve activity. In Holloway's series the von Graefe sign was present in 80 per cent of patients with primary toxic goitre, in 66 per cent of patients with secondary toxic goitre and in 33 per cent of patients with simple goitre.

If the von Graefe sign is not apparent on first examination of a patient with hyperthyroidism, it may often be evoked by repeated trials—the phenomenon of Kocher. Occasionally it is noted that the upper lid moves by jerks on elevation and depression of the eye—the sign of Boston.

*Stellwag's sign* Infrequency of winking was first described as a symptom of primary toxic goitre by Stellwag in 1869 (9). The rate of winking in the normal eye is about four times per minute. In primary toxic goitre this is occasionally reduced to twice per minute, or even to longer intervals. The infrequency of winking appears to augment the expression of fixed stare. This sign is, however, comparatively rare. Von Szily (10) believes Stellwag's is closely related to the presence of exophthalmos.

*Joffroy's sign* When the eyes are rotated upwards, normally there occurs a synergistic contraction of the levator of the lids, and a contraction of the frontalis with concomitant wrinkling of the skin of the forehead. In some cases of primary toxic goitre, especially those characterized by a positive von Graefe's sign, this synergistic action is disturbed. The frontalis does not contract and there is an absence of the wrinkling of the skin of the forehead. This symptom was first described by Joffroy in 1893 (11).

*Gifford's sign* This was first described by Gifford in 1906 (12). It consists of difficulty in eversion of the upper lid. In the normal individual looking down with the eyes closed, the upper lid is readily everted by grasping the cilia at the lid margin and using slight pressure with a small rod at the upper edge of the tarsus and turning the lid on this as a fulcrum. In patients with primary toxic goitre such eversion of the upper lid may be extremely difficult, if not impossible. In his original description, Gifford noted there was an apparent puckering of the skin of the upper retro-tarsal fold. He noted that this sign occurred early in the course of hyperthyroidism, was independent of the degree of exophthalmos, and frequently disappeared as the disease became advanced and the exophthalmos pronounced.

*Rosenbach's sign* This little-mentioned sign is essentially tremor of the closed lid. As originally described by Rosenbach (13), when patients with this sign are told to close their lids, there is a spasm like contraction of the frontalis and facial muscles, the lids do not close forcibly, and there is no appearance of folding of the skin of the eyelids. The lids either blink repeatedly or, with the lid margins barely touching, go into a tremor.

*Pathogenesis of the palpebral signs* The immediate cause of the various palpebral signs encountered in primary toxic goitre is obviously a disturbance of the lid opening closure apparatus. To understand the mechanism of this muscular disturbance, the general anatomy, action and innervation of the various muscles concerned in the opening and closure of the lids may be reviewed.

The voluntary elevator of the upper lid is the levator palpebrae superioris. The muscle, composed of striate fibers, arises at the apex of the orbit and extends forward in the shape of an isosceles triangle, lying above the superior rectus muscle. In the fore part of the orbit, the belly of the muscle terminates in an expanded tendon known as the "aponeurosis". The anterior edge of this breaks up into fine connective fibers, which radiate upwards and downwards and are inserted in the skin of the lids anterior to the tarsal plate (Fig 1). The levator is innervated by the upper division of the oculomotor, or third cranial nerve. Closure of the lids is accomplished by contraction of the orbicularis oculi (Fig 11), an oval thin sheet of striate muscle covering the eyelids and circum orbital region. The orbicularis is innervated by the seventh cranial nerve. There is an antagonistic activity between the levator and the orbicularis, with a balanced tonus, contraction of the levator being accompanied by a relaxation of the orbicularis and vice versa.

In addition to these two voluntary striate muscles there are also involuntary smooth muscles in both the upper and lower lids, which influence the width of the lid slit. These are the tarsal, or palpebral involuntary muscles, first de-

scribed by Mueller in 1859 (14), and bear his name. They must not be confused with Mueller's orbital muscle, also described by the same author the previous year. In the upper lid, the superior palpebral involuntary muscle is well developed, being about 1 cm broad in its antero-posterior length. It lies immediately beneath the aponeurosis of the levator, its fibers arising from between the striated fibers of the levator. The fibers pass downward beneath the aponeurosis and insert by fine fibers in the upper posterior portion of the tarsal plate (Fig. III). The action of the superior palpebral involuntary muscle is to elevate slightly the upper lid and retract the upper edge of the tarsus. In the lower lid the inferior palpebral involuntary muscle is much less distinct. The fibers arise from the fascicular sheath of the inferior rectus or from the prolongation

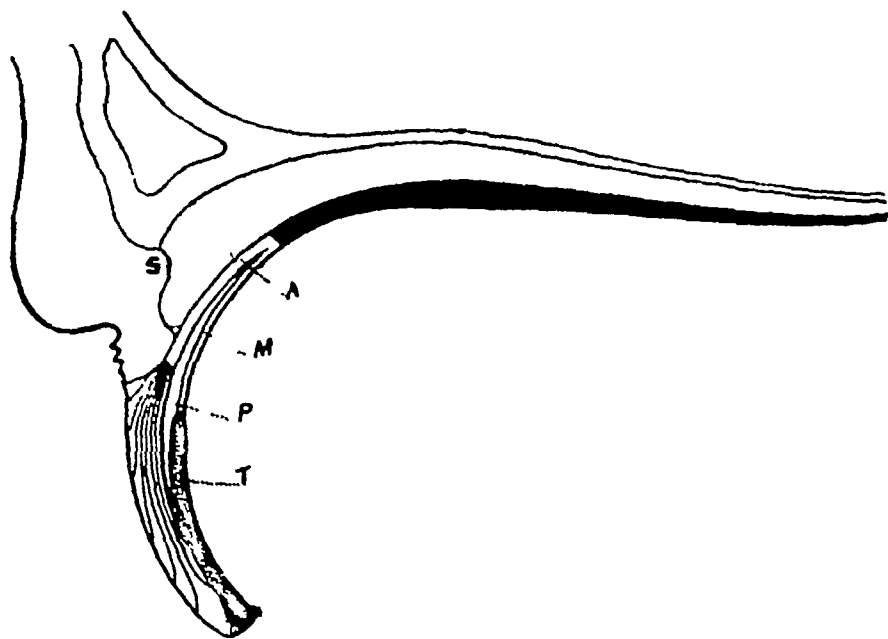


FIG. I. DIAGRAM ILLUSTRATING LEVATOR PALPEBRAE SUPERIORIS AND MULLER'S PALPEBRAE MUSCLE

A = Aponeurosis of Levator, M = Mueller's palpebral muscle, P = Pretarsal Space, T = Tarsal plate (After Whitnall)

of this sheath over the superior oblique. The fibers pass forward, dividing into two lamellae at the conjunctival fornix. One sheet ends in the bulbar conjunctiva, while the other enters the lower lid and inserts just short of the lower edge of the tarsal plate in the fascia. The combined action of these upper and lower involuntary tarsal muscles is to widen the lid slit. Both the superior and inferior involuntary palpebral muscles are innervated by the sympathetic system, probably by fibers direct from the cavernous plexus which enter the third nerve at its point of division in the upper and lower branches.

While it is obvious that the various lid signs of primary toxic goitre are produced by some disturbance in the normal lid opening and closure apparatus, the nature of the disturbance, the factors which initiate it, and the possible influence of a concomitant exophthalmos are not so clear.



Dalrymple, as early as 1834, stressed the importance of the levator and actually believed that in addition to retracting the upper lid it also had a subsidiary action of slightly protruding the globe (15). Von Graefe, in 1864, in describing the lid sign which bears his name, attributed it to a spasm of the involuntary palpebral smooth muscle. Stellwag, in 1869, assumed that relaxation of the orbicularis was the cause of the various lid symptoms. The mechanism of the various palpebral signs is, however, probably more complicated than assumed in these early explanations. The possible rôle of an exophthalmic globe producing pressure changes on the musculature and nerve endings in the lids has been



FIG II DISSECTION SHOWING ORBICULARIS OCULI  
(After Whitnall)

frequently mentioned. Since, however, all the lid signs of primary toxic goitre can occur without exophthalmos, the latter, when present, must be considered at best but an augmenting mechanical factor.

The complexity of the old opening-closure theory is illustrated by certain clinical and experimental observations of Poos (16). Poos started with the assumption that the involuntary palpebral smooth muscle had no real dynamic function, but only a static or contractive function. By experiments with pharmacological and electrical stimulation of the nerves in animals with various combinations of experimental sympathetic and facial paralysis, he was able to show that under certain conditions relaxation of the orbicularis was accompanied not only by some overaction of the levator but also by activity of the involuntary

palpebral smooth muscle, producing a prolonged widening of the lid slit. There was also a concomitant or preceding dilatation of the pupil, indicating the activity of the cervical sympathetic system. A similar phenomenon occurs in emotional crises in man. In addition, Poos showed that in patients with primary toxic goitre there was relative relaxation of the orbicularis. In a case of unilateral exophthalmos in primary toxic goitre, this orbicularis relaxation was present only on the affected side.

The basic cause of this disturbance in the lid closure-opening apparatus of patients with primary toxic goitre probably lies in increased instability of the sympathetic nervous system, a sympathicotonia, coupled with certain reflex relaxations or contractions of the voluntary muscle, the exact nature of which is not clear, but may or may not be related to pressure by the exophthalmic



FIG III DISSECTION SHOWING MUELLER'S PALPEBRAL MUSCLE

A = Aponeurosis of levator, M = Mueller's muscle, T = Tarsal plate (After Whitnall)

globe. Primarily, it is well known that disturbance in one link of the endocrine chain produces changes in the other glands of internal secretion, and there is pharmacological evidence of increased adrenal action in some thyrotoxic patients (17). It is also a matter of universal observation that organs supplied by the adrenergic nervous system, the heart, vascular apparatus, etc., show an increased excitability in thyrotoxicosis. The assumption of an increased tonus of the involuntary palpebral smooth muscle through stimulation of the cervical sympathetic has therefore been advanced.

The possibility of a central nervous system involvement has been brought up by numerous authors. Rollet and Ficment (18) pointed out that the von Graefe symptom occurred not only in hyperthyroidism, but was also seen occasionally in Parkinson's disease and with conjugate paralysis of the upward gaze. Velhagen (19) pointed out that in post-encephalitic Parkinson's disease there might occur not only a von Graefe sign, but also the other eye signs of

hyperthyroidism, a Dalrymple, Stellwag or Moebius sign, and quoted *Economo's* explanation that these were due to lesions in the extra pyramidal tract in the neighborhood of the third ventricle. Velhagen also suggested that concentration of thyroxin in the tuber cinereum might account for the secondary nervous manifestations of thyrotoxicosis, basing this suggestion on the work of Chittenhelm and Eisler (20). Other authors (21) place the site of the original stimulation in the diencephalon, with resulting sympathetic irritation, believing that a lesion there may be the actual cause of practically all the eye signs of hyperthyroidism.

Whatever may be the primary cause, the immediate course of the palpebral signs of primary toxic goitre is a disturbance of the lid closure-opening apparatus, involving the orbicularis, the levator, and the palpebral smooth muscles. Varying degrees of involvement of these muscles offer an explanation of all the lid signs of toxic goitre.

The Dalrymple sign would be produced by a relaxation of the orbicularis, a compensatory over action of the levator and a tonic contraction of the involuntary palpebral smooth muscles to maintain the widening of the lid slit and produce the fold in the upper lid. The von Graefe sign, as originally stressed by von Graefe, would depend chiefly on tonic contraction of the involuntary palpebral smooth muscle. Stellwag's sign would obviously be due to atony or relaxation of the orbicularis. Joffroy's sign would be due to over action of the levator, coupled with a disturbance of the synergistic action of the frontalis. Gifford's sign would depend primarily upon the tonic spasm of the involuntary palpebral smooth muscle. Rosenbach's sign would be produced by a weakness or relaxation of the orbicularis, the muscle going into tonic contraction on forced closure.

Exophthalmos should be regarded only as a contributing or augmenting factor. Undoubtedly the majority of the lid signs reach their maximum development in the presence of an exophthalmos, which in itself forcibly widens the lid slits and produces pressure on the orbicularis. As von Szily points out in his admirable monograph, the cause for the lid symptoms in hyperthyroidism must be sought for in the following factors, present in varying degree: Kinetic—relaxation of the orbicularis and contraction of the levator. Static—tonic contraction of the involuntary palpebral smooth muscles. Mechanical—the pressure on the lids by the protruding globe.

## II. EXTERNAL OCULAR CHANGES IN HYPERTHYROIDISM

The four widely different external ocular signs grouped under this heading are Moebius' sign, Jellinek's sign, Loewi's sign and excessive lacerimation. The four signs have nothing in common with the exception that the last two may be dependent on sympathetic irritation.

*Moebius Sign* (22) This is weakness of convergence. Of all the eye signs of hyperthyroidism this is of the most doubtful diagnostic significance. Weakness of convergence is found in individuals with myopia, exophoria, unilateral amblyopia, etc., and frequently as an isolated muscle imbalance in otherwise

normal individuals. Holloway and his co-authors give the incidence of convergence weakness as 10 per cent in primary toxic goitre, as 40 per cent in secondary toxic adenoma, and as 1.4 per cent in patients with simple adenoma of the thyroid. On the other hand, Sattler believes that when other usual causes are ruled out, convergence weakness is an extremely rare ocular complication of hyperthyroidism. When present in primary toxic goitre it is not related to the presence of degree of exophthalmos and cannot be regarded as dependent on a mechanical stretching of the recti muscles. It has been suggested that Moebius' sign is due to a central lesion in the basal ganglia, similar to the changes in Parkinson's disease, that it is a symptom of myasthenia, or that it may be due to organic infiltration changes in the internal recti muscles. As a matter of fact, its entity as a sign of hyperthyroidism is doubtful, and its cause is unknown.

*Sign of Jellinek* (24) This is an abnormal pigmentation of the skin of the lids and may be associated with similar pigmentation of the nipples and genital organs. It is comparatively infrequent, and when present usually occurs early in the course of hyperthyroidism. The pigmentation resembles somewhat that of Addison's disease, and suggests some concomitant involvement of the adrenals as the cause. This sign was first described by Rosin and Jellinek in 1900 (23), and again by Jellinek in 1904 (24). It is occasionally alluded to as Rosin's sign.

*Loewi's sign* This sign is the dilatation of the pupil sometimes observed in primary toxic goitre patients when adrenalin is instilled into the conjunctival sac. It is assumed to be an evidence of hyper-irritability of the sympathetic endings in the smooth muscle dilator fibers of the iris. The phenomenon was first described by Loewi in 1908 (25), who observed such a dilatation of the pupil in an animal with experimental pancreatic deficiency. He suggested that in hyperthyroidism such a reaction might be evidence of an adrenalin hyper-irritability caused by thyrotoxicosis.

*Excessive lacrimation* This interesting phenomenon may occur quite early in primary toxic goitre, and may even precede the onset of the hyperthyroid symptoms by several months (26). It is apparently an infrequent ocular complication, although there are a number of isolated cases reported in the literature (27). It was first described by Wilbrand and Saenger in 1901 (28), and almost at the same time by Berger (29). It was believed by Wilbrand and Saenger that the epiphora was due to overaction of the lacrimal gland through irritation of the trigeminus and sympathetic fibers supplying it, and by Berger to be a manifestation of sympathetic hyper-irritability. It is apparently independent of an exophthalmos or any malposition of the puncta. It may occur only at night. Gifford noted that it might persist after all the general metabolic evidence of hyperthyroidism had disappeared and therefore suggested that it might be due to an anterior pituitary hormone acting directly on the lacrimal gland. A similar suggestion was made by Wahlberg (30). The histological examination of a lacrimal gland from a patient with primary diffuse toxic goitre was reported by Reese (31), who found a chronic dacryo-adenitis, with areas of degeneration and edema throughout the gland, and collections of lymphocytes,

the picture being strikingly similar to the changes sometimes observed in extra-ocular muscles

### III EXTRA OCULAR PALSIES

These are among the more serious of the ocular complications. Extra-ocular paralyses in hyperthyroidism were first noted by Naumann (32) in 1853, and again described by Ballet (33) in 1888. They are sometimes known as Ballet's sign. Since Ballet's paper they have been reported and discussed by innumerable authors. They are among the rare complications of primary toxic goitre, according to Heuer (34) occurring in only one of every 300 cases.

The extra ocular palsies of hyperthyroidism may be divided into two groups:

1. Isolated or multiple palsies, associated with severe thyrotoxicosis and exophthalmos, which together with the exophthalmos disappear with the subsidence of the metabolic phases of the hyperthyroidism.
2. Ocular palsies, either isolated or multiple, often affecting muscle groups which move the eye in a definite plane and are always associated with exophthalmos, but usually without severe thyrotoxicosis, which persist with the exophthalmos after all the metabolic evidences of the hyperthyroidism have disappeared. The second group has been described under a number of different names and is perhaps best known by the term applied by Brain "exophthalmic ophthalmoplegia."

I. The ocular palsies in the first group usually affect individual muscles, although they may affect several muscles and may even progress to a complete unilateral or bilateral ophthalmoplegia externa, with or without ptosis. There is no marked preference of involvement for any of the extra-ocular muscles in this group, although it is frequently stated that there is a tendency for elevation of the eye to be first impaired, with palsy of the superior rectus, the external rectus, internal rectus, and obliques being later involved. The isolated paralyses are often bilateral and may affect different muscles in the two eyes. They practically never occur without a concomitant exophthalmos. If the exophthalmos recedes and the thyrotoxicosis is controlled either by subtotal thyroidectomy, or iodine and other medical treatment, the paralyses disappear.

The cause of these muscular palsies is not clear. Schiff-Wertheimer and Justin Besancon (35), believe the cause is mechanical due to a weakness and stretching of the extra-ocular muscles. This would explain the greater involvement of the superior rectus muscle, since it is the shortest of the four recti muscles. It would also explain the frequent absence of any paralysis of the levator. It would not explain, however, the fact that very high degrees of exophthalmos may be present without any paralysis or obvious weakness of any of the extra-muscles.

Other authors have attributed the extra-ocular palsies to organic changes in the muscles themselves. That organic changes may occur in the voluntary striate muscle in primary toxic goitre was first established by Askanazy (36), in 1898. This investigator studied the striate muscles of the body, including the orbital muscles, in patients with exophthalmic goitre and found that a lymphocytic infiltration with interstitial fibrosis might occur in all muscles

excepting the cardiac musculature, as will presently be noted. Such changes may occur in an advanced degree in the extra-ocular muscles, especially in the exophthalmic ophthalmoplegia group. These extreme changes are, however, quite rare or entirely absent in the first group of isolated palsies. Mulvany (37), who divides the ocular changes of hyperthyroidism into a "thyrotoxic" and a "thyrotropic" group, believes this first group of isolated palsies are dependent on specific organic changes produced by the thyrotoxicosis, the changes being quite unlike those occurring in the "thyrotropic", or exophthalmic ophthalmoplegia group. The extra-ocular muscles, Mulvany points out, are somewhat specialized, with fine striae and extensive nerve endings, and like other



FIG IV EYE MUSCLE IN SEVERE THYROTOXICOSIS

Wasting of muscle fibers with irregularity in size, shape and density (M F), and degeneration of new supply (N F) (After Mulvany)

highly specialized tissues, are especially subject to toxic influences. Under thyrotoxicosis these muscles undergo a special form of degeneration, consisting of general wasting and irregularity of the muscle fibers, extensive and severe degeneration of the abundant nerve supply (Fig IV), with loss of striation of the muscle fibers, granulation of the sarcoplasm and reduplication of the sarcolemmal nuclei (Fig V). This, he believes, is a thyrotoxic myasthenia, to be sharply differentiated from myasthenia gravis. Against this view, is the fact that the biopsy of the extra-ocular muscles in patients with primary toxic goitre frequently shows entirely normal muscles. It is also not yet clear if the changes described by Mulvany in the "thyrotoxic type" are not early manifestations of the changes found in the thyrotropic or exophthalmic ophthalmoplegia.

Still other authors have suggested that changes in the ocular muscles were analogous to those so frequently seen in myasthenia gravis. Along this line Wedd and Permer (40) reported clinical observations and autopsy findings in an exophthalmic goitre patient with ophthalmoplegia and ptosis. The authors

found changes in the thyroid, adrenal and thymus and believed the ocular palsies were due to a concomitant myasthenia gravis. Cohen and King (41), on the basis of a review of the literature and their own cases noted that similar disturbances—lymphatic hyperplasia, suprarenal involution, lymphorrhagia in the muscles, lymphocytosis, decreased carbohydrate tolerance—were found both in exophthalmic goitre and myasthenia gravis, and suggested similar endocrine and metabolic disturbances were responsible for both diseases. Naffziger and Jones noted the similarity of the histological changes in the muscles found in myasthenia gravis. Thorner (42) noted that when symptoms of thyrotoxicosis and myasthenia occurred together, the symptoms of thyrotoxicosis

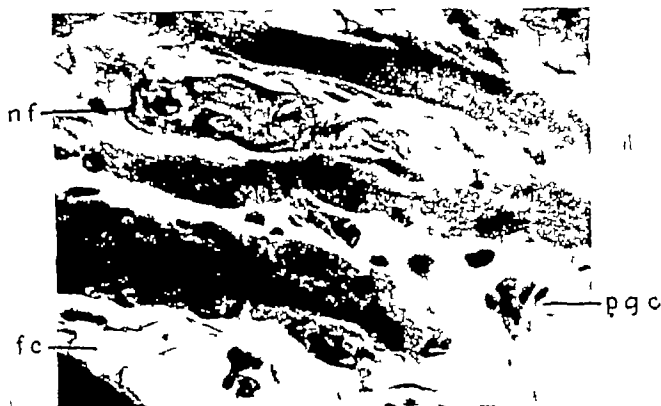


FIG. V. EYE MUSCLE IN THYROTOXIC OPHTHALMOPLÉGIA

Loss of striation of muscle fibers granulation of sarcoplasm and reduplication of nuclei. Regenerated nerve husk (N.F.) Fat cells (F.C.) Pseudo-giant cells (P.G.C.) due to breaking down of muscle fibers (After Mulvany)

were at a maximum when those of myasthenia were at a minimum—a possible explanation of the frequent persistence of the ocular palsies after subsidence of the metabolic symptoms.

Somewhat in favor of myasthenia changes being responsible for the ophthalmoplegias occasionally observed in exophthalmic goitre is the well known autopsy finding that patients with exophthalmic goitre usually show enlarged thymus glands, and the results achieved in myasthenia gravis by removal of the thymus gland (43). However, the suggestion that a concomitant myasthenia gravis may be the cause of these extra-ocular palsies is based solely on rather indefinite clinical and histological observations, and definitely against the relationship of these palsies to myasthenia gravis is the observation that prostigmine has no effect on them.

The suggestion that the palsies may be due to a central lesion has been occasionally advanced. This however would assume separate lesions for the

third, fourth and sixth nuclei, and offers no adequate explanation for the constant involvement of the levator, and the constant absence of an ophthalmoplegia interna, when other third nerve muscles are involved

It is therefore impossible at this time to attribute any specific and definite cause to the extra-ocular palsies of primary toxic goitre. There is considerable evidence that organic changes in the muscles may be a responsible factor and that other local causes, such as stretching and weakness of the muscles or the general orbital edema which may accompany the exophthalmos, may be contributing factors. The possibilities of a central lesion produced by thyrotoxicosis, or a concomitant myasthenia gravis dependent on a related endocrine dysfunction, are somewhat more remote.

II Exophthalmic Ophthalmoplegia—Malignant Exophthalmos—Progressive Exophthalmos after Thyroidectomy. Under these names there has been described a remarkable and not altogether infrequent syndrome, the essential feature of which is a progressive or persistent exophthalmos, usually associated with ocular palsies, moderate thyrotoxicosis and sometimes a relatively low basal metabolic rate, the exophthalmos and the ophthalmoplegia often become more intense when the general metabolic phases of the disease are controlled by medical treatment or thyroidectomy. In some cases of hyperthyroidism, a thyroidectomy may actually precipitate the development of such an exophthalmic ophthalmoplegia. Jensen (45) described the disease under the name of malignant exophthalmos, Brain (46) and other English authors under the name of exophthalmic ophthalmoplegia, and Thomas and Woods (39) and later Ginsburg (47), as progressive exophthalmos after thyroidectomy and Means (48) as Graves disease with dissociation of thyrotoxicosis and ophthalmopathy. It is now usually spoken of as "exophthalmic ophthalmoplegia" and it has been claimed it is a syndrome separate from Graves disease. It corresponds however to the "thyrotropic" type of exophthalmos of Mulvany, and the "ophthalmic" type of Rundle and Wilson.

Cases of exophthalmic ophthalmoplegia have been reported by numerous authors. The exophthalmos may become so extreme that covering of the eyes by the lids becomes impossible. The cornea becomes dry and opaque, as in keratitis and lagophthalmos, secondary ulceration occurs and the eyes may be lost (37, 39, 49). Even after bilateral enucleation of the eyes the orbital contents may continue to increase in size until redundant masses of orbital tissue covered with conjunctiva protrude through both lid slits (39).

The diagnosis of exophthalmic ophthalmoplegia after thyroidectomy has been performed obviously offers no difficulty. The pre-operative diagnosis requires a careful examination of the eyes and the recognition of certain points in which the protrusion of the eyes and the ocular symptomatology differ from the usual exophthalmos of primary toxic goitre. These points are as follows. In the early stages the degree of protrusion may be slight, but it usually progresses until it becomes extreme. It may be unequal on the two sides. Whether the exophthalmos is slight or extreme, it is usually accompanied by chemosis, swelling of the lids, reduction in motility of the eye and disturbances in muscle



co-ordination, symptoms of epiphora, hyperemia and edema of the conjunctivae, photophobia and a sensation of hard resistance when the effort is made to reduce the exophthalmos by pressure on the globes. The extra-ocular paralyses and disturbances of muscle co-ordination which are a part of exophthalmic ophthalmoplegia have certain peculiarities, especially emphasized by Brahm. These are the frequent involvement of muscle groups moving the eyes in one plane, especially elevation. Only rarely is the ophthalmoplegia total, usually isolated muscles, or combinations of the recti and obliques being affected. The usual thyrotoxic lid signs are absent, edema being the main symptom. Impairment of vision from optic neuritis is relatively common. Hertz (50) believes the

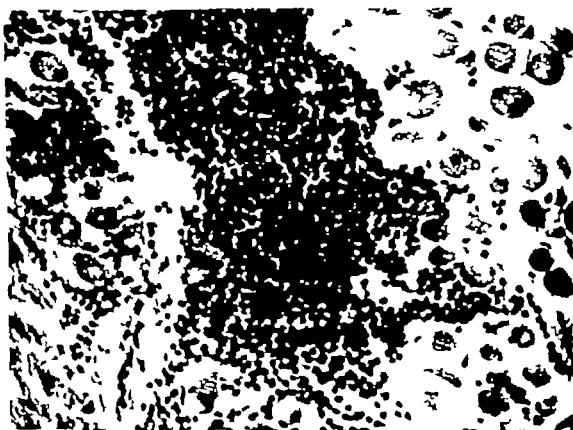


FIG. VI. EYE MUSCLE IN EXOPHTHALMIC OPHTHALMOPLÉGIA

Chronic myositis. Interstitial fibrosis. Islands of lymphocytes. (High power.)

important points in the early diagnosis of such cases are the relatively small size of the goitre, the predominance of ocular complaints, the rapid and super-standard response to iodine, and the marked edema.

Histologically the extra-ocular muscles in exophthalmic ophthalmoplegia usually show marked changes. These changes were described by Burch (51) in 1929, and were carefully studied by Naffziger in 1931 (52), by Friendenwald (38), Thomas and Woods (39), and Krönfeld (53). The changes are essentially a hypertrophic myositis, the hypertrophied muscles at times enlarging as much as eight times the normal size. They show a chronic myositis with interstitial fibrosis and edema with islands of round cells suggesting lymphocytic germinal centers.

The immediate cause of the ocular palsies in this group appears to lie in the organic changes in the muscles, especially the fibrosis, probably accelerated by the stretching of the muscles from the high degree of exophthalmos usually

present. This latter factor, the exophthalmos, may explain the frequency of involvement of both superior recti muscles.

The pathogenesis of exophthalmic ophthalmoplegia is not clear. Means (54) believes the ocular picture is a local manifestation of a generalized metabolic abnormality in which a fundamental disturbance of body water and electrolytes is concerned. On the other hand the diminished secretion of normal thyroxin may have an irritating effect on the anterior pituitary and allow an over production of the hypothetical hormone which acts on the orbital contents. Daniels (55) believes the original cause is a disturbance in the diencephalon, possibly precipitated by some endocrine dysfunction in the adrenals or gonads. This activates the anterior pituitary by way of the hypothalamus. The clinical evidence of the occurrence of exophthalmic ophthalmoplegia in patients with



FIG VII EYE MUSCLES IN EXOPHTHALMIC OPHTHALMOPIEGIA  
(Low power)

low basal rates, and the improvement often noted following the administration of iodine and thyroid extract, both indicate that exophthalmic ophthalmoplegia is not associated with hyperthyroidism and thyrotoxicosis, or with an increased secretion of normal thyroxin, but rather with hypothyroidism or a deficient secretion of normal thyroxin. Indeed Maine (56) has suggested that the exophthalmos of exophthalmic ophthalmoplegia may be quite different from the usual exophthalmos of primary toxic goitre, being produced by organic changes in the orbit, actual hyperplasia of the orbital contents, and especially hypertrophy of the extra-ocular muscles, while the exophthalmos of primary toxic goitre is produced more by edema than actual organic hyperplasia of the orbital contents. Somewhat similar views were expressed by Aird (57) as a result of his investigations on the experimental exophthalmos produced by injections of anterior pituitary extract. He believed that in exophthalmic oph-



FIG VIII DECOMPRESSION OF ORBIT BY MODIFIED KROENLEIN APPROACH  
SHOWING POSITION OF SKIN INCISION AND RECESSION OF EXOPHTHALMUS  
[A Preoperative exophthalmus 33 norm] [B Post operative] [C Lateral View]

thalmoplegia (malignant exophthalmos) the real cause of the exophthalmos lay in a degenerative and fibrotic myopathy, and that this change was the result of the failure of the patient to establish a proper endocrine adjustment after the thyroidectomy.

The treatment of exophthalmic ophthalmoplegia depends on the stage in which the disease is recognized and on the degree of exophthalmos and exposure of the eyes. If recognized before thyroidectomy, medical treatment rather than operation is indicated. As far as the ocular prognosis is concerned the patients usually do better if not subjected to thyroidectomy, which sometimes appears to augment violently the eye symptoms. In patients with progressive exophthalmos after thyroidectomy the administration of iodine and thyroxin in sufficient amount to increase the basal rate to +10-15 has been tried although favorable reactions are not constant. Deep gamma ray or x-ray irradiation of the orbit and even of the hypophysis has been tried occasionally with some success. If iodine, thyroxin, and irradiation are unsuccessful, operative interference may be necessary to save the eyes. Such local operative interference may be either palliative or radical. The palliative procedures are designed to reduce the chemosis and protect the cornea. If the edema of the conjunctiva is so intense that it threatens the nutrition of the cornea, wedge excision of the chemotic conjunctiva has been recommended (58). If the lids cannot be voluntarily closed sufficiently to protect the cornea, lateral tarsorrhaphy to decrease the size of the lid slit and to permit closure is often sufficient, but any tarsorrhaphy must be guarded lest the orbital pressure be thus further increased by the backward pressure of the lids and a vicious cycle be initiated. If the exophthalmos is too great for tarsorrhaphy to be successful, the only other procedure possible is the more radical one of orbital decompression. This may be accomplished either by the removal of the temporal wall of the orbit (59), or by the Naffziger operation. The removal of the temporal wall of the orbit is best done by placing the skin incision well back in the hair line, dissecting forward the skin and subcutaneous tissue over the temporal muscle, opening the periosteum over the outer margin of the orbit and resecting the lateral bony wall of the orbit (60). The orbit is thus decompressed in the zygomatic fossa. This gives an excellent cosmetic result with marked relief of the exophthalmos (Fig VIII). The Naffziger approach consists in the resection of the roof of the orbit and opening the canal of Zinn by the transfrontal pituitary approach, decompressing the orbit into the cranial cavity (61-62).

#### IV. EXOPHTHALMOS

Exophthalmos may occasionally be one of the initial symptoms of primary toxic goitre, although as a rule it follows the vascular disturbances, the tremor and the increase in the basal metabolism. The various statistical reports indicate it is present in from 40 to 90 per cent of all cases of primary toxic goitre, the mean being 65 per cent.

The degree of exophthalmos is determined by measuring the actual distance of the apex of the cornea from the mid-line of the bony margin of the orbit at

the external canthus. This may be done either by sighting laterally along a millimeter rule, or by one of the various exophthalmometers, Hertel's (Fig IX) being somewhat more accurate, while Ludde's (Fig X) has the advantage of simplicity.

In the normal individual the antero-posterior distance from the external margin of the orbit to the apex of the cornea varies between 12 and 14 mm, occasionally running as high as 16 mm. It is greater in myopes than in hyperopes. A protrusion of over 16 mm in the absence of high myopia is regarded

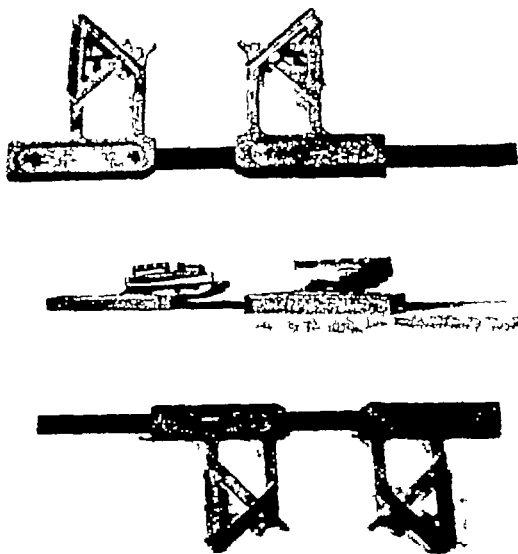


FIG IX HERTEL'S EXOPHTHALMOMETER

as pathological. Exophthalmos may, of course, be caused by a variety of conditions other than primary toxic goitre—orbital neoplasm, orbital inflammation, arterio venous aneurysms, cavernous sinus thrombosis, tenonitis, etc.

The exophthalmos of primary toxic goitre may be unilateral but is more often bilateral, although often of different degrees in the two eyes. It usually varies between 16 and 24 mm. When greater than 24 mm the retracted lids may actually slip behind the equator giving the ghastly picture of almost complete exposure of the bulbs. In high degrees of exophthalmos, vision is threatened by desiccation and clouding or ulceration of the exposed cornea. Exophthalmos *per se* does not as a rule produce changes in the optic nerve, although in the extreme of the progressive exophthalmic ophthalmoplegia group when there is marked orbital edema, pressure changes may occur in the

optic nerve These changes usually begin as a blurring of the neuroretinal outlines, then actual elevation of the nervehead (Fig XI), produced by venous stasis from the orbital hyperplasia In the late stages of exophthalmos prolonged pressure may produce actual death of the nerve fibers with secondary optic nerve atrophy Papilloedema and optic atrophy are, however, rare complications of the exophthalmos of primary toxic goitre

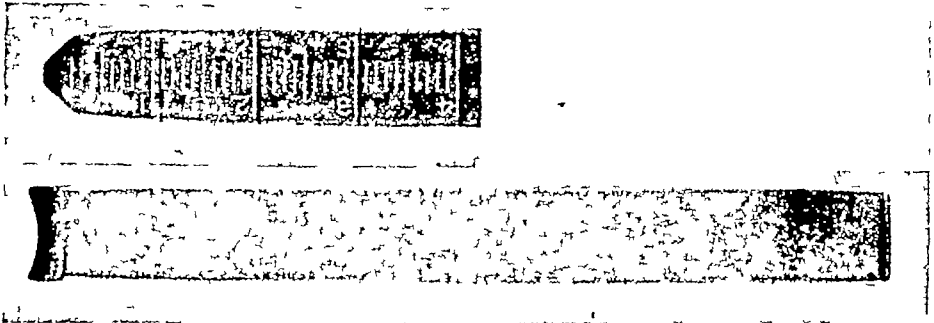


FIG X LUDDE'S EXOPHTHALMOMETER



FIG XI PAPILLOEDEMA IN EXOPHTHALMIC OPHTHALMOPLÉGIA

It is generally believed that, with the exception of the exophthalmic ophthalmoplegic or thyrotropic group, the exophthalmos of primary toxic goitre regresses after control of the metabolic phase of the disease Recent studies by Grace and Weeks (63) and by Soley (64) cast some doubt on this commonly accepted belief Grace and Weeks reported there was no change in the exophthalmos following sub-total thyroidectomy in 80 patients with toxic goitre Soley studied in detail 106 patients with exophthalmos and primary diffuse toxic goitre and followed 78 of these patients over a period of at least 5 years following sub-total thyroidectomy or irradiation of the thyroid Any changes in the exophthal-

mos of these patients was measured with the Hertel exophthalmometer. In approximately 50% of these patients there was an actual average increase of 1.5 mm. in the exophthalmos following treatment. In only a small percentage (less than 10%) was there any actual regression of the exophthalmos. Soley pointed out that from the cosmetic view, point, however, the exophthalmos appeared to have regressed. Thus he believed due to the disappearance of the "stare," the widening of the lid slits (Dalrymple's sign). Soley did not divide his patients on the basis of exophthalmic ophthalmoplegic, thyrotoxic or thyrotropic, or thyroid and ophthalmic types. Somewhat similar conclusions were reached by Galli Mainini (65), who measured any changes in the protrusion of the eyes in 126 patients with various types of thyroid disease. He found that in patients who had been recognized to have had exophthalmos during the active phase of their disease, some degree of it always persisted thereafter when measurements were made.

It is frequently stated in the literature that the exophthalmos of primary toxic diffuse goitre disappears after death. To check the accuracy of this statement the hospital and autopsy records of patients dying in the Johns Hopkins Hospital from primary toxic diffuse goitre were reviewed. There were fifty such case records. These records showed that in eleven patients there was no exophthalmos, in nine others only slight exophthalmos, while in the remaining thirty the clinical notes reported moderate or severe exophthalmos. In twenty-two of the thirty patients with exophthalmos, 73 per cent, the pathologist noted moderate or advanced exophthalmos at the time of autopsy. In one case, autopsied 84 hours after death, the pathologist reported that extreme exophthalmos persisted. In the light of this checkup it appears clear that the oft-repeated statement that the exophthalmos of primary toxic goitre recedes after death is an error.

### *Pathogenesis*

The various theories advanced to explain the exophthalmos of primary toxic goitre may be grouped under the following general heads—

- 1 Hypertrophy of the orbital contents
- 2 Relaxation of the striated extra-ocular muscles
- 3 Contraction of the smooth muscles of the orbit or lids
- 4 Simple edema of the orbital contents
- 5 Dilatation of orbital blood vessels
- 6 Hypertrophic myositis of orbital muscles
- 7 The action of an anterior pituitary hormone on the orbital contents

These various theories may be summarized as follows

1 *Hypertrophy of the Orbital Contents* In his original description of the symptomatology of the disease which so often bears his name, Basedow (66) suggested that exophthalmos was dependent on an actual strumous hypertrophy or hyperplasia of the orbital contents, especially the fat. The accuracy of this early observation has been confirmed by histological study of the orbital contents of patients with exophthalmos from primary toxic goitre and in exoph-

thalmoplegia Smelser's (67) analysis of the orbital contents in both clinical and experimentally produced exophthalmos indicates there is a general hyperplasia of the orbital contents in which the fat particularly participates. However accurate was Basedow's original observation, it offered no explanation for the fundamental mechanism which initiates the exophthalmos. It is peculiar that fat should be deposited in the orbit in a disease characterized by a general wasting of the fat elsewhere throughout the body.

II *Relaxation of the striated ocular muscles* In 1849 (6) Cooper suggested that the exophthalmos of primary toxic goitre resulted from a relaxation of the four recti muscles, thus allowing either the normal orbital pressure or some additional factors to displace the eyes forward. Various modifications of this idea have cropped up since then. Fisher (68) in 1921 suggested that the degeneration in the extra-ocular muscles in exophthalmic goitre produced a relaxation of the recti muscles which was a contributory factor in the exophthalmos. However, any theory which attributes the exophthalmos to a weakening of the extra-ocular striate muscles without some added factor, overlooks the fact that the eyeball is normally held in a state of equilibrium by the tonicity of the extra-ocular muscles, the four recti acting as retractors, being antagonized by the obliques which act as protractors. Any loss of tonicity in these muscles would affect both the recti and the obliques and would therefore leave the eye in a state of "status quo", and would not explain the exophthalmos. Such a factor has been postulated by Mulvany, who believes a relaxation of the extra-ocular striate muscles is a contributing cause in one form of thyroid exophthalmos—the so-called thyrotoxic type (see below). He describes actual organic changes in the extra-ocular muscles, a so-called thyrotoxic myasthenia which produces a weakening and relaxation of the muscles. According to his idea, these changes, in conjunction with a contraction of an orbital smooth muscle produces exophthalmos in the thyrotoxic group.

A peculiar variation of this original relaxation theory has recently been introduced by Spektor (69). He advanced the novel idea that the eye in primary toxic goitre is forcibly pulled forward by a contraction of the obliques. Spektor hypothesized a "stretching" center, a lesion of which permitted relaxation of the recti muscles. This relaxation or stretching of the recti muscles, coupled with a contraction of the obliques, produced exophthalmos. It is not clear, however, why the recti should stretch and the obliques contract.

III *Contraction of the Smooth Muscle of the Orbits and Lids* This neuromuscular theory assumes that the exophthalmos of primary toxic goitre is produced primarily by excitation of the cervical sympathetics with resulting contraction of smooth muscle fibers in the orbit, thus either pulling or pushing the eye forward while a secondary venous obstruction causes orbital edema.

The genesis of this idea lies in an observation of Claude Bernard (70) in 1852, who observed that stimulation of the cervical sympathetic in animals produced widening of the lid slits, dilatation of the pupil and exophthalmos. In 1858 Mueller (71) described smooth muscle fibers on the floor of the orbit. These fibers are known as Mueller's orbital, or the peri-orbital, muscle, and must not



be confused with Mueller's palpebral muscle. In animals this peri-orbital muscle is quite a definite entity. In the quinea pig it completes the lateral wall of the orbit, and in the dog and cat it extends laterally and envelops the posterior portion of the eye in a muscular cone. In man, however, this peri-orbital muscle is a vestigial affair and is represented only by a few bundles of smooth muscle fibers, which cover the superior aspect of the infra-orbital fissure. In its greatest extent it is only 2 to 3 mm wide, deeper in the center, and fan-shaped at its extremities, where it spreads in a thin layer over the orbital floor. Posteriorly it may reach back to the annulus of Zinn where some of its fibers may be related to the ophthalmic vein. Through this small sheet of muscle fibers pass a few small venules. This peri-orbital muscle is innervated by the cervical sympathetic. The only apparent action of the muscle is to tense the fascia of the orbital floor.

The evidence in favor of Mueller's orbital muscle being concerned in exophthalmos is as follows —

Mueller, himself, believed that contraction of this peri-orbital muscle in man caused exophthalmos in man, although his early death prevented the presentation of any supporting experimental or clinical evidence. In 1868 (72) a group claimed that stimulation of the cervical sympathetic in man caused widening of the lid slit, dilatation of the pupil and exophthalmos. Carefully controlled experiments on the dog and cat in 1904 (73), 1915 (74) and 1935 (75) all clearly showed that stimulation of the cervical sympathetic produces a constriction of the peri-orbital smooth muscle cone and a marked protrusion of the eyes in the animals. The experimental exophthalmos occurred even in the animals which were decapitated and the head washed free of blood, indicating the independence of the exophthalmos from venous stasis. However, venous stasis was still believed to be a factor in the toxic exophthalmos in man. Later anatomical researches (76-77) on the eyes of stillborn children indicated that a contraction of Mueller's orbital muscle might conceivably cause such venous stasis. Thus Kraus and Frund reported that the development of the peri-orbital muscle in man was subject to some variations, that at times it might extend along the floor of the orbit between the main venous branches, and by its contraction produce a venous stasis, the degree of which might vary not only in different individuals, but might even vary in the two eyes of the same individual.

Despite this evidence, the objections to this neuro-muscular theory appear to be insurmountable. Primarily, notwithstanding the early claims to the contrary, stimulation of the cervical sympathetic system in man does not produce exophthalmos. This has been shown by innumerable experiments on the living subject from 1862 (78) to the present time (79) and is aptly illustrated in the somewhat gruesome experiment of Wagner in 1858 (80). Wagner obtained, immediately after death, the head of a young woman executed by decapitation and stimulated the cervical sympathetic. There resulted a widening of the lid slit and dilatation of the pupil, but no exophthalmos. Further, the experiments illustrating the production of exophthalmos in the dog and cat by stimulation of the cervical sympathetic are not applicable to man where there is a great

anatomical difference and Mueller's orbital muscle is only a vestigial structure. The exhaustive anatomical researches of Hesser in 1913 (81) showed conclusively that in man Mueller's orbital muscle was represented only by a few smooth muscle fibers over the infra-orbital fissure, and transversed only by a few small venules. Contraction of these fibers could not conceivably alter the position of the eye, and compression of the small venules transversing the muscle could not materially alter the volume of the venous blood in the orbital system, since there are free and numerous anastomoses with the veins of the face. Finally, exophthalmos has been reported (82) in primary toxic goitre occurring in patients with a pre-existing complete paralysis of the cervical sympathetic. On the basis of the available clinical and anatomical evidence, it therefore seems impossible to attribute to Mueller's orbital muscle any role in the production of the exophthalmos of primary toxic goitre.

A variation of the neuro-muscular theory was brought forward by Landström in 1907. His idea was that exophthalmos was not produced either by a contraction of the orbital smooth muscles and a pushing forward of the eye or by venous stasis secondary to such contraction back of the eye but by contraction of independent smooth muscle fibers around the anterior ocular segment. Landström reported (83) that in addition to the muscles discovered by Mueller in 1858, there was another smooth muscle in the orbit, which he described as follows — "The anterior portion of the eyeball is surrounded by a cylindrical muscle, consisting of smooth fibers, with origin at the orbital septum and insertion at the equatorial region of the eye where it is connected with fascial bands derived from the extra-ocular muscles." The cylinder is not quite complete in so far as it is interrupted at the uppermost parts of the eyeball in the region of the levator palpebrae superioris. Landström believed that contraction of these smooth muscle fibers forcibly dragged the eye forward. It is contraction of this supposed muscle, coupled with contraction of Mueller's involuntary palpebral muscle, and a toxic myasthenia of the extra-ocular muscles that Mulvaney believes is responsible for the exophthalmos of his thyrotoxic type. However, Hesser was unable to confirm the presence of any such smooth muscle, and completely discarded this theory. Troell (84), who believed the smooth muscles in the anterior portion of the orbit might be concerned in exophthalmos, was likewise totally unable to confirm Landström's findings, and believed Landström had been dealing with a few aberrant fibers of Mueller's palpebral muscle. However, even were the so-called Landström's muscle an anatomical entity, its contraction would appear more likely to retract the yielding tarsal plate posteriorly rather than drag forward the eye.

*IV Edema of the Orbital Contents* The theory of orbital edema was advanced in 1911 by Sattler (85), who pointed out the fallacies of all theories which sought to account for the exophthalmos of primary toxic goitre on the grounds either of relaxation of the striate muscles of the orbit, contraction of the smooth muscles, or venous stasis. He believed the cause of exophthalmos lay in a simple orbital edema similar to the edema in the lids, and secondary to capillary or arteriolar dilatation, such as is seen in the face of many patients with exoph-

thalmic goitre In a case of exophthalmic goitre he reported the histologic study of the orbit showed a definite edema, and pointed out that toxins could produce a selective orbital edema, citing as an instance the edema and exophthalmos resulting from the injection of paraphenyldiamine in dogs The fact that the exophthalmos was believed to decrease after death was advanced by Sattler as evidence in favor of this edema theory As already pointed out, this often repeated statement appears to be an error Sattler advanced no explanation of the cause of the edema other than a selective toxic action on the orbital tissue

As will presently be pointed out, histological studies of the orbits of patients with exophthalmic goitre and of rabbits with experimentally produced exophthalmos, have clearly shown that edema fluid is at least one of the components of the increased orbital bulk Galli-Mainini (65) has offered the hypothesis that in thyrotoxicosis the organism is maintained at the upper limit of its water regulating capacity The edema of the orbit in thyrotoxicosis may be explained by the following mechanism In health the normal tension of the extraocular muscles maintains a certain intra-orbital pressure In thyrotoxicosis, due to the weakness of the muscles which accompanies the disease, there is a relaxation of the recti muscles, a corresponding drop in the intra-orbital pressure, and an escape of fluid from the vessels into the orbit This state of affairs may be aggravated by other edematogenic factors, such as increased pulse pressure, decreased osmotic pressure, dilatation of the capillaries and increased capillary permeability

*V Dilatation of the Orbital Blood Vessels* Vasodilatation of the orbit as the factor responsible for the exophthalmos of primary toxic goitre has been advanced by a number of different authors, and was strongly advocated by E Fuchs (86) This theory assumes that as a result of the thyrotoxicosis there is a general disturbance of the vascular innervation, especially of the cervical sympathetic system As a consequence there occurs a dilatation of the vessels in the carotid bed and often an actual visible pulsation of the carotid arteries The distention of the arterial vessels in the thyroid gland is one factor in the enlargement of the thyroid, and the vasodilatation in the orbital tissues causes an increase in the orbital volume contents and results in an actual protrusion of the eye As a further support of this theory, the oft-repeated statement that exophthalmos recedes after death is advanced

However, this relatively simple explanation does not fit all the known facts The essential objections to Fuchs' theory are (A) congestive phenomena in the eye and orbit are present only in the relatively few cases of the exophthalmic ophthalmoplegia type (B) that vasodilatation in the orbital bed would not account for the histological picture of excess orbital tissue (C) that orbital veins have no valves and do have numerous anterior and posterior communications, and (D) that the exophthalmos certainly does not constantly recede after death

A variation of the vaso-dilatation theory has been advanced by Zappacosta (87) Attracted by the earlier experiments of Labbé and his coworkers (95, 96)

which indicated that in some cases of hyperthyroidism there might be a para-sympathetic excitation component, Zappacosta advanced the idea that this para-sympathetic activity might play a decisive part in the exophthalmos of primary toxic goitre. The mechanism of this he conceived to be as follows: the para-sympathetic activity caused a hyperemia of the retro-bulbar vessels. This orbital congestion in the presence of a simultaneous sympathetic activity, acting presumably on the orbital smooth muscle, lead to the protrusion of the eyes. Thus in the production of exophthalmos, activity of both branches of the autonomic nervous system was therefore necessary. In support of the presence of para-sympathetic activity in primary toxic goitre, in addition to the pharmacodynamic experiments of Labbé and his coworkers, he cited the work of Hess, Eppinger and Faltau. In support of a sympathetic over-activity as a factor in the production of exophthalmos he cited the work of Justin-Besançon (88), who observed that the administration of yohimbin, a sympathetic depressant, caused a regression in the exophthalmos of an experimental animal, and of Sloer (89), who observed the same phenomenon in patients with exophthalmos of primary toxic goitre. However, much against the theory of Zappacosta is the emphasized statement of Justin-Besançon that the exophthalmos produced in experimental animals by the injection of combination of thyroxin with sympathetic and para-sympathetic exciting drugs occurred without any evidence of dilatation of the orbital or retinal vessels.

*VI Degenerative Myositis* The degenerative myositis with fibrosis of the ocular muscles has already been described. These changes produce a marked increase in the size of the muscle, up to three to eight times its normal size. Naffziger and Jones have suggested that this hypertrophy of the extra-ocular muscles may be a contributing factor in exophthalmos, or may be the actual cause of the progressive exophthalmos that sometimes follows thyroidectomy.

While it is undoubtedly true that this hypertrophy of the extra-ocular muscles frequently occurs, it appears unlikely that such a muscle change could *per se* be the actual cause of exophthalmos, although in many cases it might well be a contributory cause. Primarily, such changes in the extra-ocular muscles are inconstant (38, 39), are present only in a relatively small number of patients, and even in progressive exophthalmos may be entirely absent. When present it is probably only an accidental phenomenon. Similar changes are observed in other muscles, especially the diaphragm, in thyrotoxicosis. It would appear that the hypertrophy of the muscles with a degenerative myositis at best could be only a contributory factor to the exophthalmos.

*VII The Action of Anterior Pituitary Hormone* The conception that the exophthalmos of primary toxic goitre is related to the action of an anterior pituitary hormone is the result of a series of experimental observations. The first group of experiments are those by Loeb and Bassett (90) in 1929, by Schockaert (91) in 1932 and by Loeb and Friedman (92) in 1932. These investigations all showed that in various species of animals the injection of an extract of the anterior pituitary gland produced with great regularity the picture of a primary toxic goitre, and in many instances a concomitant exophthalmos.

The nature of the exophthalmos, its relation to the hyperthyroidism and to irritation of the cervical sympathetic, was then investigated by Marine (88) and his co-workers, and later by Smelser and others, with somewhat conflicting results. First Marine (93) and his associates showed that the injection of both methyl cyanide and anterior pituitary extract independently would under certain conditions cause in experimental rabbits a thyroid hyperplasia and often an exophthalmos. If the experimental animals were thyroidectomized prior to the injection, the exophthalmos occurred with great regularity. In the thyroidectomized animals the development of exophthalmos might be somewhat inhibited by feeding the animals fresh green vegetables or by the administration of iodine and thyroxin, and could be prevented by extirpation of the cervical sympathetic ganglion. They therefore concluded the cyanide and pituitary exophthalmos were produced by the same means, namely excitation of the cervical sympathetics and contraction of Mueller's orbital muscle. The excitation of the sympathetic was caused by an anterior pituitary hormone, in the one instance secreted by the experimental animal as a result of the cyanide injection, and in the second case by direct administration of anterior pituitary extract. They believed the development of this exophthalmos was somewhat dependent on a relative thyroid deficiency, and could thus be prevented by the maintenance of a normal thyroid balance through the administration of iodine and thyroxin (94).

Marine and his co-workers then advanced the following suggestion to explain the exophthalmos of primary toxic goitre (94). They pointed out, as is generally recognized, that there is a delicate balance between the various endocrine glands—the adrenal cortex, the gonads, the anterior pituitary, and the thyroid. Especially is there a physiological balance between the secretion of the thyrotropic hormone and the thyroxin need of the body. A disturbance in the hormone secretion of the adrenal cortex or the gonads might result in a compensatory over activity of the anterior pituitary, with resulting hyperplasia of the thyroid from oversecretion of the thyrotropic hormone, and exophthalmos resulting from excitation of the cervical sympathetic system. The increased secretion of thyroxin, however, tends to inhibit the exophthalmos, either by controlling the activity of the anterior pituitary, or possibly by some indirect inhibitory action on the cervical sympathetic. The lack of thyroxin, such as is present in thyroidectomized animals, removes this inhibitory factor and allows full development of the exophthalmos.

The immediate objection to this suggestion is that, even granting excitation of the cervical sympathetic and contraction of Mueller's orbital muscle is the mechanism of the anterior pituitary exophthalmos in animals, such a mechanism would not be possible in man where Mueller's orbital muscle is only a vestigial structure. This point was later admitted by Marine (95). In favor of a possible gonadotropic influence are the observations that exophthalmos is more common in men than in women, and in the experimental rabbit the anterior pituitary exophthalmos may be checked by castration of the animal and later accelerated by the administration of testosterone propionate (96).

The question of the possible role of the cervical sympathetics and Mueller's muscle was, however, greatly cleared by the investigations of Smelser (97) These investigations, which began in 1936, may be summarized as follows

It was first determined that injections of anterior pituitary extract in normal guinea pigs produced an intense stimulation and enlargement of the thyroid with accompanying loss of body weight, but practically no exophthalmos Thyroidectomized guinea pigs similarly treated with anterior pituitary extract developed marked exophthalmos, beginning as a rule from twelve to twenty days after the start of the treatment This exophthalmos did not disappear post-mortem The development of the exophthalmos in thyroidectomized guinea pigs was uninfluenced either by the extirpation of the cervical sympathetic ganglion, or by the prior surgical removal of Mueller's orbital muscle

A study of the orbital contents of these guinea pigs with experimental exophthalmos showed a 28-30 per cent actual increase in the weight of the orbital contents of the exophthalmic pigs over that of the controls All of the tissues of the orbit, with the exception of the ventral lacrimal gland, participated in this hyperplasia, there being 100 per cent increase in the fatty connective tissue, 40 per cent increase in the dorsal lacrimal gland, and a 22 per cent increase in the size of the extra-ocular muscles

Histologically the retrobulbar contents of the exophthalmic rabbits showed an infiltration of edematous material penetrating into the loose connective tissue and among the fat cells This material stained with eosin and aniline blue and contained granules and droplets as well as many lymphocytes scattered through the tissue Fig XII shows the orbital contents of a guinea pig with experimental exophthalmos, contrasted with the orbital contents of a normal guinea pig (Fig XIII) The extra-ocular muscles showed an irregular involvement, usually only one or two muscles being affected, with nests of lymphocytes and infiltration of the same edematous material observed in the fatty tissue This is shown in Fig XIV, contrasted with the normal extra-ocular muscles of a guinea pig (Fig XV)

A comparison of the orbital contents of patients who had died with exophthalmic goitre, with the orbital contents of the guinea pigs with experimentally produced anterior pituitary exophthalmos, showed the same general picture in both groups In the human cases Smelser found a general reaction through the orbit with edema and wandering cells in the fat, connective tissue, and muscles The edematous material appeared as a smooth material staining with eosin and aniline blue, penetrating between the collagenous connective tissue, and in some instances between fat cells which appeared isolated in an eosinophilic medium (Fig XVI), in contrast with a normal human orbit (Fig XVII) The wandering cell invasion of the orbit of the human exophthalmos (Fig XVIII) was quite similar to that of the guinea pig with experimental exophthalmos (Fig XIX) The changes in the extra-ocular muscles were also similar in both groups, in the human cases the muscle fibers being separated by an interstitial edema, together with infiltration with wandering cells (Fig XX), while the same picture is found in the experimental guinea pig (Fig XIV)

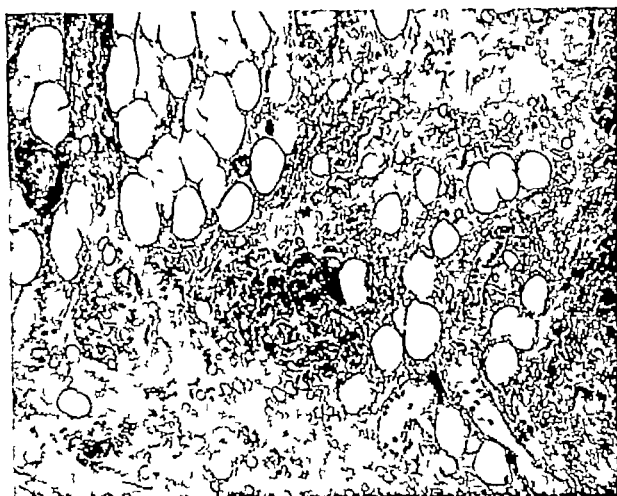


FIG XII ORBITAL TISSUE IN EXOPHTHALMIC GUINEA PIG  
Oedematous infiltration of fat and connective tissue Round cell infiltration (After Smelser)

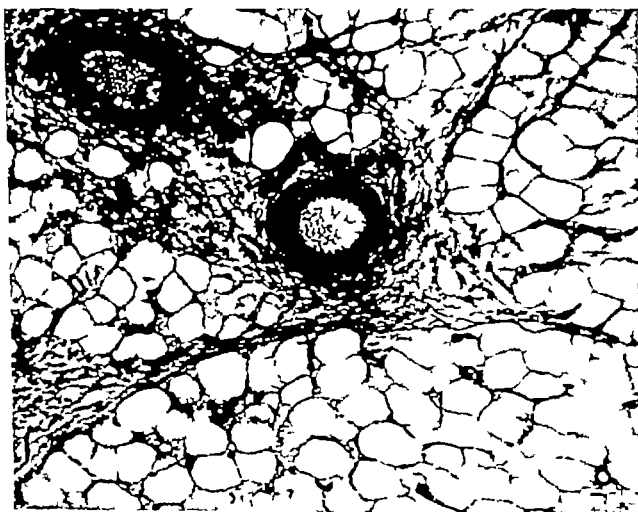


FIG XIII ORBITAL FAT OF NORMAL GUINEA PIG  
A region particularly rich in connective tissue (After Smelser)

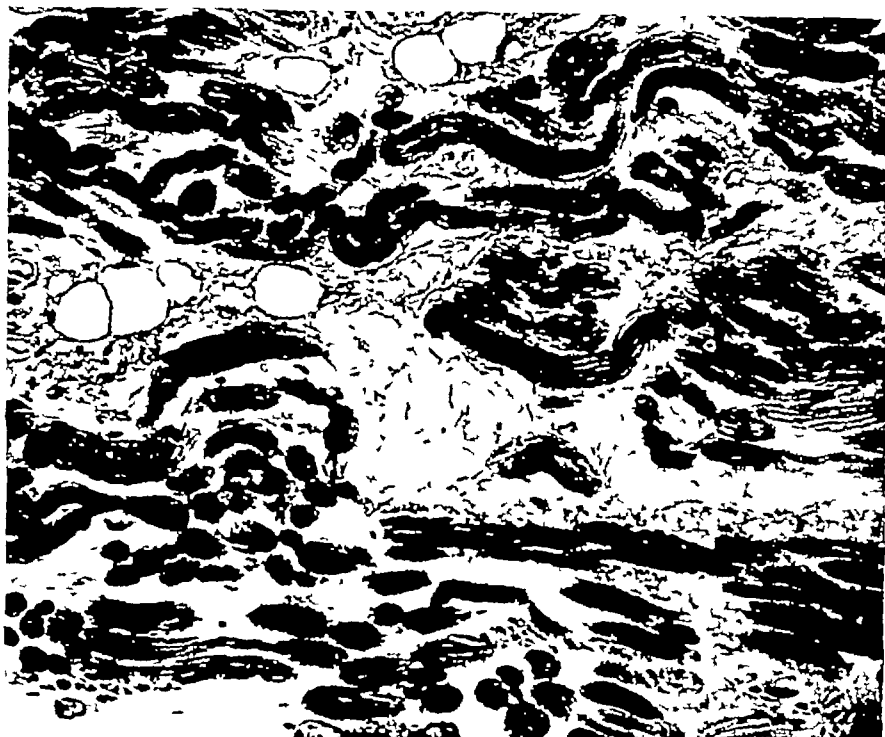


FIG XIV OCULAR MUSCLE OF EXOPHTHALMIC GUINEA PIG

Segmentation of muscle fibers, infiltration of oedematous material with fatty tissue and lymphocytes (After Smelser )

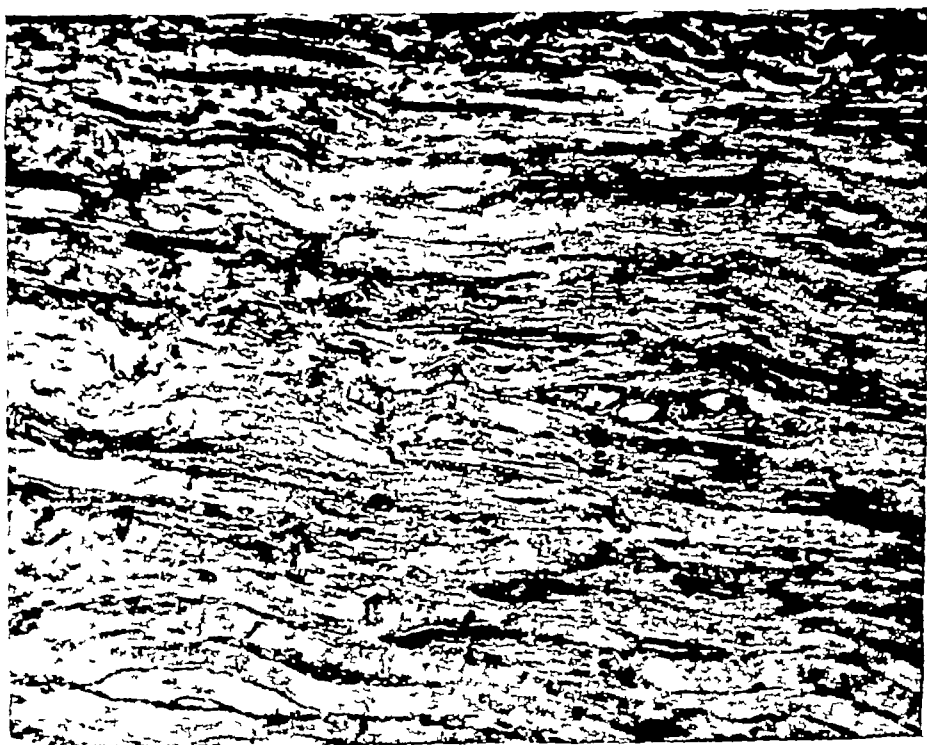


FIG XV NORMAL EXTRA-OCULAR MUSCLE OF GUINEA PIG  
(After Smelser)



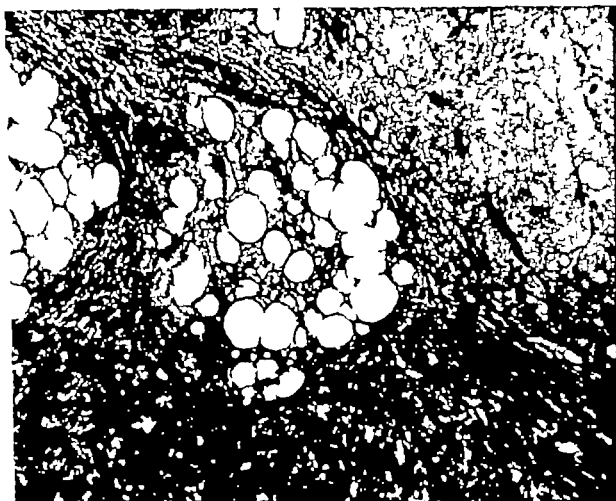


FIG XVI ORBIT OF HUMAN EXOPHTHALMIC GOITRE  
Oedematous infiltration of fat and connective tissue Round cells throughout section

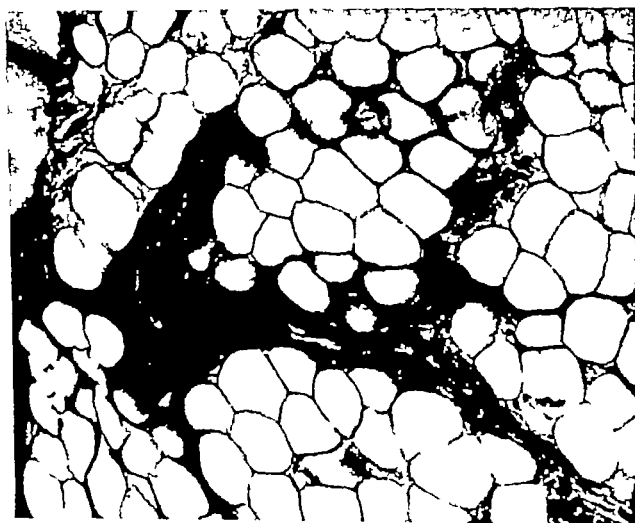


FIG XVII NORMAL HUMAN ORBITAL FAT  
(After Smelser)

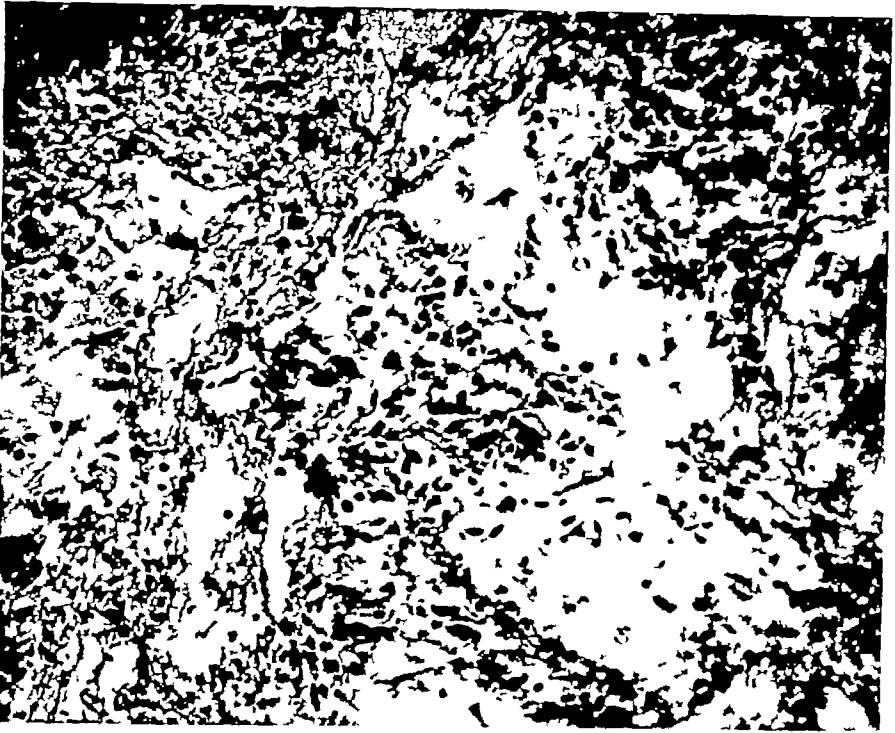


FIG XVIII WANDERING CELL INVASION OF ORBITAL TISSUE OF HUMAN  
EXOPHTHALMIC GOITRE  
(After Smelser)

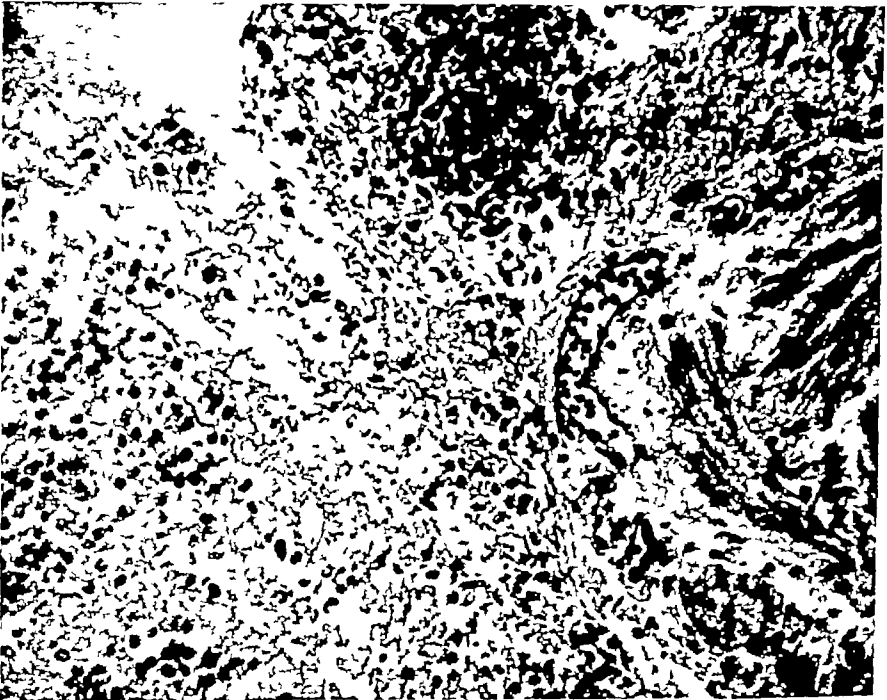


FIG XIX WANDERING CELL INVASION OF ORBITAL TISSUE OF EXPERIMENTAL  
EXOPHTHALMIC GUINEA PIG  
(After Smelser)

Smelser also studied the effect of iodine, thyroxin and diiodotyrosine on this experimental exophthalmos and on the orbital contents. He found that the injection of sodium iodide in the main produced a decrease in the size of the orbital contents through a diminution in the size of the dorsal lacrimal gland. The ingestion of sodium iodide or diiodotyrosine produced no effect. On the other hand the ingestion of thyroxin produced a definite decrease in the entire orbital contents, all the orbital tissue being involved in the weight loss. The injection of thyroxin likewise partially inhibited the action of anterior pituitary extract in producing an exophthalmos, the incidence of exophthalmos in the thyroidectomized guinea pigs receiving both anterior pituitary extract and



FIG XX. OCULAR MUSCLE OF HUMAN EXOPHTHALMIC GOITRE

Oedema between muscle fibers and round cell infiltration. Compare with Fig XIV (After Smelser)

thyroxin being 52 per cent against 86 per cent in the animals receiving the anterior pituitary extract alone.

Smelser concluded that there was a marked similarity between the experimental exophthalmos produced by anterior pituitary injections and the clinical exophthalmos of primary toxic goitre. He believed that in neither instance was the exophthalmos related to venous stasis, sympathetic irritation, or to contraction of the orbital smooth muscle. The actual cause of exophthalmos was an enlargement of the orbital contents due to interstitial edema, an increase in the adipose tissue, and in the volume of the muscles associated with some cellular infiltration. This enlargement of the orbital contents was in some manner secondary to the action of the anterior pituitary, but whether through action of the thyrotropic hormone or some other hormone was not clear. Normal

thyroxin has apparently an inhibitory effect on the development of the orbital hyperplasia. He disagreed with the work of Maine and his associates that the exophthalmos produced by methyl cyanide was due to stimulation of the anterior pituitary, and believed it was in no way comparable to the experimental anterior pituitary exophthalmos or the clinical exophthalmos of primary toxic goitre.

Smelser's work on the production of exophthalmos in normal and thyroidectomized guinea pigs, and on the edema of the orbit and degenerative changes in the muscles was confirmed later by Paulson (98). The subject was also further investigated by Aird (56). Using the ordinary alkaline commercial preparations of anterior pituitary extract, Aird reported that daily injections produced an initial thyrotoxicosis followed by a refractory period, during which the exophthalmos occurred. In the extra-ocular muscles of these guinea pigs he found apparently with great regularity the histologic changes emphasized by Naffziger. He then injected guinea pigs with purified extract of the thyrotropic hormone of the anterior pituitary, and again obtained thyrotoxicosis and exophthalmos in normal guinea pigs, but found this extract did not produce exophthalmos in thyroidectomized pigs. On the possibility that some hormone other than the thyrotropic might be concerned in the production of the exophthalmos produced by anterior pituitary extract, he injected a series of animals with a purified adienotropic hormone, but no exophthalmos resulted. A further analysis of the anterior pituitary extract ruled out the gonadotropic, mammatropic and the growth hormones as etiological factors in the production of exophthalmos. Aird concluded that this experimental exophthalmos was related to the thyrotropic hormone, and the early histological changes of edema were identical in the experimental anterior pituitary exophthalmos and the exophthalmos of primary toxic goitre. Likewise the prolonged administration of anterior pituitary extract to experimental animals produced the degenerative and fibrotic myopathy he believed characteristic of malignant exophthalmos, or exophthalmic ophthalmoplegia.

A somewhat different view of the mechanism of exophthalmos is taken by Mulvany. Primarily he divides hyperthyroidism into three separate entities, —a thyrotoxic type being an expression of hyperthyroidism and sympathicotonia, a thyrotropic type dependent on pituitary control, and a thyriopathic type, exemplified by such local thyroid disease as early neoplasm, infection or lymphadenoid goitre. Only in the thyrotoxic and thyrotropic types does exophthalmos occur, and these two types of exophthalmos can be sharply differentiated.

The exophthalmos of thyrotoxicosis he believes due to two factors. These are (A) a sympathicotonia producing a combined spastic contraction of Landstom's muscle, the existence of which Mulvany accepts, and Mueller's orbital muscle, and (B) the specialized myasthenia of the extra-ocular muscles due to thyrotoxicosis, and already described. The characteristics of thyrotoxic exophthalmos are a normal orbital content, the absence of intra-orbital oedema and pressure, the spastic retraction of the lids together with other eye signs of sym-

pathictonia, and the quite different type of degeneration of the extra-ocular muscles.

The exophthalmos of thyrotrophic origin is due to a straightforward increase in the orbital contents, with the hypertrophic and pathologic changes in the muscles noted by Burch and Naffziger. The pathogenesis of these changes may be due to several components, notably the coincident presence of increased quantities of the thyrotrophic hormone and certain sterones, notably testosterone. Mulvany suggests that the specific action of the male hormone and maybe of other sterones on striped muscle may be altered by thyrotropin. He cites the well known muscular hypertrophy accompanying virilism or resulting from testosterone administration, and offers the assumption that the thyrotrophic exophthalmos may be quite similar in both experimental animal and in man, being the expression of a disturbance of both the thyroid and sex secretions. In any event, the changes in the orbit result in increased intraorbital pressure, pushing the eye forward against the lids and starting a vicious cycle. The patients show both hyperthyroidism and exophthalmos, but the prime factor is the action of a pituitary hormone on the orbital contents. The symptomatology of this form of exophthalmos and of the thyrotoxic exophthalmos is quite different. In the thyrotrophic variety there is an incipient stage in the development of the exophthalmos which usually lasts one or two years, but may be much shorter. This is followed by a second stage of a few weeks or a few months in which the exophthalmos rapidly increases. The third stage is that of malignant exophthalmos with corneal ulceration. The general subjective symptoms are pain in the eyes, varying from a throbbing ache up to an intense ophthalmic neuralgia, lacrimation, photophobia, and diplopia due to a gradually developing ophthalmoplegia. The physical signs are protrusion bulbi, often greater on one side than the other, retraction of the upper lid, due not to neuro-spasm but chiefly to mechanical pressure on the levator from the enlarged muscle cone, disturbances of muscle co-ordination, affecting usually the superior recti from pressure, and due also to increased intra-orbital pressure and degenerative changes in the swollen muscles, and lastly a local vascular alteration, beginning with a dilatation of the conjunctival vessels and progressing up to bagginess and finally true oedema of the lids and conjunctiva, often associated with congestive changes in the optic nerves and retina. The seven differential points shown by thyrotrophic exophthalmos, and absent in thyrotoxic exophthalmos, are the subjective phenomena, an unequal development of the exophthalmos, the absence of true lid spasm, the frequently higher degree of proptosis, the sensation of hard resistance when an effort is made to reduce the exophthalmos, the presence of congestive features and lastly the rarity of fixation of the globes.

Mulvany questions the clinical entity of exophthalmos ophthalmoplegia. He believes the cases so reported belong either to the thyrotoxic or thyrotropic group, in the first case being dependent on the specific neuromuscular degeneration he described, and in the second case dependent on pressure arising from the hypertrophied orbital contents.

In support of these views on the mechanism of exophthalmos and the ophthalmoplegia associated with hyperthyroidism, Mulvaney reviews the literature and cites experimental work which supports his views. Thus he cites the work of Labbé and his co-workers (99 and 100), and of Santon and Hesse (101), who reported the production of exophthalmos in rabbits by the combined administration of thyroid extract and sympathetic stimulating drugs, and Plummer's and Wilder's studies on the combination of weakness in the quadriceps femoris and presumably the extra-ocular muscles, and the degree of exophthalmos, work which is of doubtful statistical value. Smelser's work on the histology of the orbital contents of exophthalmic patients is dismissed with the statement such cases were "thought to have Grave's disease," and Hesser's and Troell's work failing to confirm the anatomical entity of Landstrom's muscle is completely ignored. Further, Mulvaney does not present factual evidence or biologic assays to support his statement that in the thyrotropic variety of exophthalmos there is an excess of the thyrotropic hormone while in the thyrotoxic type there is no such excess. His description of the "thyrotropic" form of exophthalmos is, however, meticulous and is quite similar to the generally accepted clinical picture of exophthalmic ophthalmoplegia.

Mulvaney's division of primary toxic goitre into two types, a thyrotoxic and thyrotropic type is not new. As already stated, the question of exophthalmic ophthalmoplegia being a distinct syndrome has repeatedly been brought up by a number of investigators. Means (48) in 1941 divided Graves disease into the "classic type", and "Graves disease with dissociation of the thyrotoxicosis and ophthalmopathy", referring to the latter as "the special ophthalmic type". In a later paper Means (104) emphasizes that no sharp line can be drawn between these two types, that in a single case the picture may proceed from one type to the other, and that in another case the sub-division cannot be made at all. Rawson's (103) work on the inactivation of the thyroid stimulating hormone by thyroid tissue indicates there is a difference in the behavior of this hormone in the two types of Graves' disease. Rawson found that the thyroid stimulating hormone of the anterior pituitary—called TSH—was inactivated by thyroid cells growing in tissue culture. Thyroid tissue from thyrotoxic patients was twice as active in this respect as the thyroid tissue from normal individuals. Studies on the thyrotropic, or TSH, activity of the urine of normal individuals, patients with low metabolic rates, and patients with thyrotoxicosis showed that there was slight thyrotropic activity in the urine of normal persons, a maximum thyrotropic activity in the urine of patients with low metabolic rates and a minimum of thyrotropic activity in the urine of patients with the usual "classic" type of thyrotoxicosis. In other words, the thyroid gland of persons with classic thyrotoxicosis has an increased power to inactivate TSH. However, this is not true with "ophthalmic type" of Graves' disease. In two patients with the "ophthalmic" type of the disease, Rawson (104) found a high thyrotropic activity in the unheated urine. He concluded that in the "ophthalmic" type of the disease, for some unknown reason, the thyroid did not respond to the TSH and inactivate it, with the result that the TSH got by activated and so escaped

in the urine. In other words, there appears to be a distinct difference in the behavior of the thyroid gland to TSH in the "classic" and "ophthalmic" types of the disease. In the "classic type" the thyroid responds to the anterior pituitary hormone with an increased output of thyroxin which in turn inactivates the TSH. In the "ophthalmic type" the thyroid does not respond to TSH, with the result the TSH is not inactivated. Theoretically, one might argue that the TSH which thus escaped inactivation, then acts on the orbit with resulting ophthalmopathy.

If these findings of Rawsons are confirmed, and a difference in the behavior of the thyroid gland to TSH in the classic and ophthalmic types of the disease is established, it would strongly support Mulvaney's division of the disease into thyrotoxic and thyrotropic types. However, the recent investigations of Rundle and Wilson (105) lend little support to such a division. These investigators examined two groups of patients with primary toxic goitre, one group with marked eye signs which they called the ophthalmic group, and the second group with marked thyrotoxicosis, with minor eye signs. They found the same general pattern of muscle disturbances in both groups, the picture being extreme in the ophthalmic group and minimal in the thyrotoxic group. They found no basis for the contention that exophthalmic ophthalmoplegia was a syndrome apart from Graves disease. They believed primary toxic goitre was an unified disease, and suggested patients be alluded to as either of the ophthalmic or thyrotoxic forms. An analysis of the orbital tissue in thyrotoxicosis by Rundle and Pochm (106) showed comparable changes in patients with and without eye signs. The changes were more marked in the ophthalmic cases and consisted of constant changes in the eye muscles, including the levator. The most marked changes were however, in the orbital fibro-fatty tissues, which they found responsible for most of the increase in bulk of the orbital contents.

A critical review of all the various theories and experiments on the etiology of the exophthalmos of primary toxic goitre permits but one conclusion—the problem is still unsolved. Notable advances, however, have been made. The clinical and modern experimental evidence indicates that exophthalmos is probably not related directly to a thyrotoxicosis and not related at all to a sympathicotonia. The weight of evidence would indicate that both the thyrotoxicosis and the exophthalmos are related in some way to the action of an anterior pituitary hormone. However, whether these reactions are due to one or several hormones is not clear. Any effect exerted by thyroxin appears, relatively at least, to influence favorably the exophthalmos, but whether by direct inhibitory action on the orbital contents or by some inactivation of an anterior pituitary hormone affecting the orbit, is again only a matter of conjecture. What rôle a deficiency in the gonads or adrenal cortex may have on the action or secretion of the anterior pituitary hormone is likewise still unknown although it may play a considerable rôle in the picture.

If the exophthalmos of primary toxic goitre is in truth initiated by an anterior pituitary hormone, the means by which it accomplishes this end is still a mystery. The anatomical evidence all points strongly to the possibility of the eye being

pushed or pulled forward by any muscular action. Edema and hypertrophy of the orbital contents with some chronic inflammatory reaction is present, but whether this is the primary cause of the exophthalmos, or is only a secondary reaction which follows the displacement of the eye forward is undetermined. Certainly if the eye were displaced forward by some other mechanism, such as a preceding dilatation of the vascular bed or by actual traction of the eye forward, edema fluid and evidence of chronic inflammation would be expected as a secondary reaction.

While there is insufficient evidence to justify the theories which assume the eye is displaced forward by action of either the striate or smooth muscles of the orbit, the question of a primary venous stasis or dilatation of the arterial and capillary bed of the orbit cannot so easily be dismissed, although there is certainly no real evidence that such occurs. Hypertrophy of the extra-ocular muscles is an inadequate explanation for the usual exophthalmos of primary toxic goitre, although it may be a contributory factor and an important factor in the exophthalmos of exophthalmic ophthalmoplegia. At present all that can safely be said is that the exophthalmos of primary toxic goitre appears to be linked up with the action of an anterior pituitary hormone, but the manner in which this hormone effects the protrusion of the eye, either by direct action on the orbital contents, through the production of some unknown metabolic toxin, through venous or arterial stasis, through some neural agency, or through some other unsuspected mechanism, is not understood. Once initiated, however, the orbital hyperplasia may continue or persist despite the control of the metabolic phases of the disease.

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# SCRUB TYPHUS IN ASSAM AND BURMA

## A CLINICAL STUDY OF 616 CASES

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1 INTRODUCTION

Scrub typhus is an acute febrile disease caused by *Rickettsia Orientalis* and characterized by a typical primary lesion, generalized lymphadenopathy, a rash, and agglutination of B Proteus OX-K by the blood serum. The pathologic

process may involve almost every organ but severer illnesses are characterized particularly by clinical signs of extensive interstitial pneumonia and meningoencephalitis. The disease has been reported from various parts of Southeast Asia, Malaya, the Dutch East Indies, Australia, Japan and certain islands of the Southwest Pacific. It is probably much more widespread than hitherto believed to be. The following paper is the report of a clinical study, based on 616 cases seen in the 20th General Hospital from October 1943 to February 1945. All these men contracted the disease in Assam and Burma, where numerous foci of scrub typhus, hitherto unsuspected, came to light during the North Burma campaign of 1943-45.

The vector of scrub typhus has been said to be a larval trombiculid mite. Other possible vectors are being studied by the U. S. Typhus Commission at this time. The animals which may act as possible reservoirs for the infection, particularly rodents, are also being investigated by them. Man to man transmission of the disease has never been reported, although laboratory infections occasionally occur.

A seasonal incidence has been suspected by some, but our cases do not support this belief. They occurred at all seasons of the year, the peaks of incidence being related to the movement of troops into certain infected areas irrespective of season.

The type of terrain where scrub typhus is contracted has been the subject of much debate. No conclusive facts have been established in this regard. However, those who have studied the problem in this area suspect (a) the grassy banks of water courses and (b) "scrub" or "man-made jungle"—cleared land with a regrowth of low jungle. The epidemiologic data we possess suggest that there are numerous localized foci in Northeastern Assam and Northern Burma where the infection can be readily acquired.

An excellent bibliography on the subject of "Tsutsugamushi Disease", as scrub typhus is called by the Japanese, has been published by Farner and Katsampes (1), which may be consulted for the details of history and epidemiology.

## 2 ORGANIZATION OF THE MATERIAL

### a *The cases*

Our 616 cases may be grouped as follows (see fig. 1).

Group 1. Eighty-one Chinese soldiers from supply or training units along the Ledo Road as far south as Shingbuiyang, Burma. Most of these appeared in the winter of 1943-4, after which time this hospital ceased to receive the majority of Chinese medical casualties. Forty of these cases have already been reported by Machella and Forrester (2).

Group 2. One hundred and thirteen American soldiers from fixed installations or positions along the Ledo Road from Lekha Pan, Assam, to Myitkyina, Burma. These consisted of a small number each month, somewhat increased during the siege of Myitkyina which took place from June to August 1944. The first 24 cases of this group have been reported (2).

Group 3 One hundred and five American patients who had been engaged in active jungle combat in the mountains east of the Mogaung Valley and north of Myitkyina from March to May, 1944. They had been subjected to privations and severe physical strain, and their evacuation was difficult and often impossible except after several days' march.

Group 4 One hundred seventy seven cases in Americans occurring in the three autumn months of 1944 among troops encamped and undergoing jungle combat training in a heavily infected focus north of Myitkyina. Facilities for immediate hospitalization and early evacuation to a general hospital were exceptionally good and the troops were in excellent physical and nutritional condition.

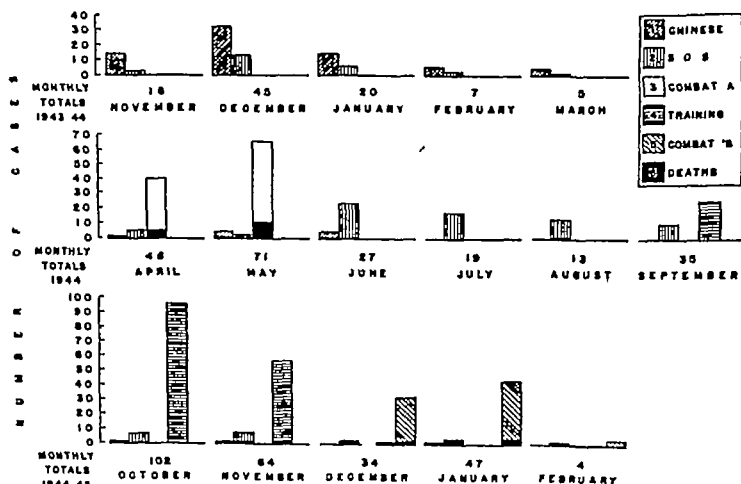


FIG. 1 MONTHLY INCIDENCE AND MORTALITY OF ACUTE SCRUB TYPHUS FROM ALL SOURCES. Cases used in the statistical series of 200 comprise the center row (April to September 1944). Most of the cases in the upper row (November 1943 to March 1944) have already been reported by Machella and Forrester (2).

Group 5 Seventy-seven American cases in December, January and February 1944-5. These men had been south of Bhamo, Burma, in jungle combat similar to, but less rigorous than, that of Group 3. Evacuation was often equally difficult and marching after the onset of fever frequently unworkable.

Group 6 In addition, 63 American patients were transferred to this hospital from other installations for convalescence or disposition.

Thus, Groups 1 and 2 might be considered "endemic cases" since they came "trickling" in more or less throughout the entire period from a wide variety of places and organizations. Groups 3, 4 and 5 might be called "epidemic cases" since they were admitted in large numbers from certain specific organizations which spent a limited time in areas presumed to be heavily infected foci. In 1944

battalion in Group 3, the incidence of scrub typhus was approximately 10 per cent of the command

The mortality of the first five groups varied from 0 per cent to 16 per cent (see Fig 1) Total mortality for the 553 patients who were acutely ill on arrival was 5.2 per cent (American 5.72 per cent, Chinese 2.4 per cent)

### *b. Methods of study*

All 616 cases were used for gathering of clinical and pathologic data. Temperature, pulse and respiration were recorded every four hours and the fluid intake and output measured during the febrile stage. Malaria smears and blood cultures on admission were routine. Semi-weekly blood counts and urinalyses were done. The Weil-Felix reaction against the three main *Proteus* strains (OX-2, OX-19 and OX-K), was done at least once a week throughout hospitalization or until a maximal titer was obtained. Regular examinations of the eyegrounds were made on all patients. Chest X-rays were done when they appeared clearly indicated. About 300 electrocardiograms were taken. During convalescence, a bi-weekly sedimentation rate became part of the routine study and stool examinations were done for ova and parasites by a concentration method.

The statistics given as percentages in the paper, unless otherwise stated, are based on 200 consecutive American patients admitted between April and October, 1944 (fig 1). These cases were studied more intensively. In addition to the above studies, the majority had Kahn tests, Widal agglutinations and stool cultures. The blood urea nitrogen was determined one or more times in 125 patients, the serum chlorides in 82, and serum protein in 43. Whenever indicated, plasma carbon dioxide combining power and prothrombin level were determined. Daily blood pressures were taken on some patients. One or more routine chest X-rays were done on over half the 200 cases. Fifty patients had electrocardiograms during the acute or convalescent phase. Weil-Felix titers were followed until they returned to insignificant levels, or, when negative, for two months.

All cases were followed well into convalescence, the majority until they were completely well. Some of the most severely ill were returned for convalescence to the United States but even these were not transported until they had been afebrile for several weeks. Patients who went back to duty usually remained in this area so that any late complications causing readmission usually reached our attention.

Of the 29 patients who died (27 Americans and 2 Chinese), 28 were autopsied. Seventeen of the deaths occurred in the statistical series of 200 cases.

### *c. Severity groups*

The published data on scrub typhus reveal a surprising variation in morbidity and mortality. This variation was seen in the various groups of our series, outlined above. The disease was basically the same in all, cases of all grades of severity occurred in each group, yet the morbidity and mortality in troops who had been through long periods of jungle combat and on short rations was much

greater than in the service troops, or in soldiers recently sent into combat or training in fixed positions. Consequently, a statistical analysis of any one of the case groups gives a distorted view of the disease (Fig 1). However, if, instead of subdividing the whole series into the various outbreaks as they were seen, they are subdivided into "severity groups" (fig 2), the disease can be discussed in a logical and coherent manner and the various clinical observations fit into a definite pattern. The mortality of the different severity groups was more or less constant so that the effects of therapy were more readily assessed, and as will be seen later the management of convalescence was simplified.

The assignment of a patient to a particular "severity group" was done fundamentally and originally on the basis of the clinician's assessment of how sick he was. When patients with similar degrees of disease severity were grouped together on this essentially subjective basis, it was found that objective criteria

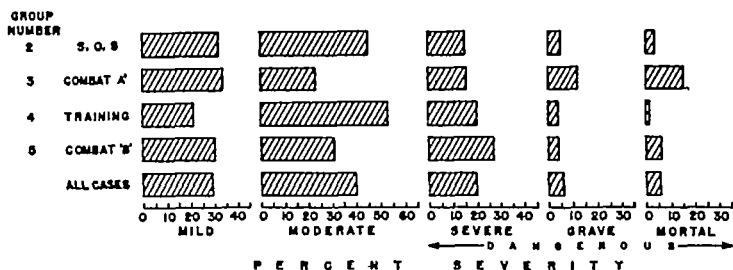


FIG 2 CLASSIFICATION OF 473 AMERICAN SCRUB TYPHUS ADMISSIONS IN TERMS OF DISEASE SEVERITY

The figures given are percentages of the total cases in each of the groups. The group numbers correspond to those given in figure 1 and in the text.

could be derived which delineated the various severity groups more definitely from one another. These criteria will be outlined in a subsequent section.

We have used the designations "mild", "moderate", "severe", "grave" and "mortal", the last three being referred to occasionally as the "dangerous" group.

### 3 THE CLINICAL PICTURE OF SCRUB TYPHUS

About two-thirds of our cases of scrub typhus completed their course after a mild or moderate illness with no clinical evidences of major dysfunction of important organs. The other third of the cases began like the former and completed their first week in much the same manner. They then developed clinical evidences of major organ dysfunction and had a stormy course which ended either in death, or recovery after a prolonged convalescence.

In order to illustrate the clinical picture of scrub typhus, we will present (a) a hypothetical or "textbook" case of moderate severity which includes all characteristic findings and diagnostic points although the co-existence of all of them in

a single individual was not common, (b) an actual case of great severity and (c) certain observations on death in scrub typhus

a "*Textbook*" picture of moderate scrub typhus

About 10 days after exposure to infection, a pink papule is found on the skin. For two or three days this becomes larger. Its top erodes. A flare develops about it. The regional lymph nodes become enlarged and tender. The patient may have headache, malaise, anorexia, weakness or no symptoms at all.

The systemic reaction then begins. Mounting diurnal fever reaches 103° or more by the third day, when the first rigor may occur. About this time generalized lymph gland enlargement begins, the nodes becoming rubbery and somewhat tender. The patient complains of aches, especially in his eye muscles, the back of his neck, the lumbosacral area and the legs. By the fourth day the face is flushed, the eyes red, the nose stuffy, the psyche apathetic. There is a dry cough. About this time the rash begins as macules on the sides of the chest or the back which rapidly increase in number and size in 24 hours and become papular. The ulcer develops a characteristic black scab covering a shallow crater with a moist yellow base.

During the remainder of the first week, the fever follows a characteristic pattern of double or triple daily spikes, marked by rigors and drenching sweats. The rash increases daily and may extend to the face, wrists and ankles. A soft spleen is palpable. So usually is the liver, and both may be tender. The first apical heart sound becomes soft. Ventilation at the lung bases is incomplete. The patient sleeps poorly. He becomes mildly confused at night and apathetic by day. He is tremulous and may be hyperesthetic.

By the tenth day the clinical picture of the disease is well established. The veins of the fundus oculi become engorged and early retinal edema may be present. The serum begins to agglutinate B. Proteus OX-K in low titer. The white blood count, which was normal or low the first week, begins to rise, and the lymphocytes increase. The mild cases begin to get well about this time (fig. 3). Their fever becomes diurnal again and falls by rapid lysis. The rash may occasionally outlast it.

The moderate case continues a little longer. A period of sustained or high remittent fever begins at some time in the second week (fig. 4). The patient becomes rapidly sicker and his condition may cause concern. Apathy is marked, and nocturnal confusion, severe. Myoclonic jerkings of the various muscle groups occur. The blood pressure often declines to 90 millimeters systolic or less. The nail-beds may be cyanotic. Rales appear at the lung bases and the respiratory rate may reach 30 per minute. The neck is stiff and sore. The heart may become top-normal in size and short periods of gallop rhythm are not uncommon. The optic disks may become blurred and diffuse retinal edema may begin. The 24 hour urinary volume may fall briefly to a pint or less regardless of intake. Coarse dark granular casts appear in the urine, together with albumin. The blood urea nitrogen may rise to 20 or 30 mgm per 100 cc. By the end of the second week the hemoglobin has fallen slightly and the Weil-Felix reaction may

be diagnostic Moderate leucocytosis may appear in some cases, with an increase in lymphocytes

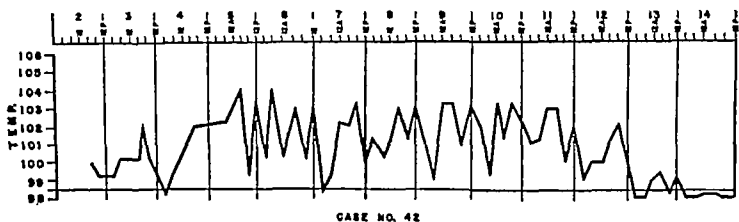
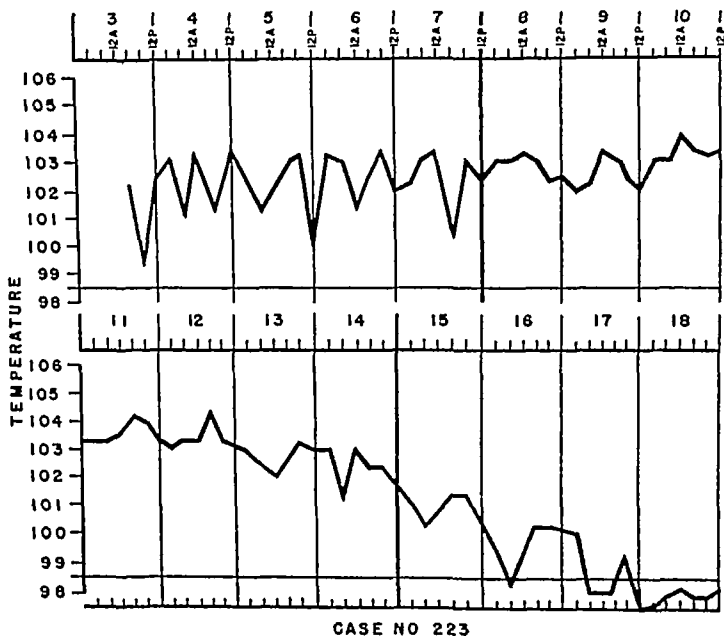


FIG 3 CASE #42 MILD SCRUB TYPHUS

The figures at the top of this and all subsequent temperature charts indicate days after the onset of fever



CASE NO 223

FIG 4 CASE #223 MODERATE SCRUB TYPHUS WITH A RELATIVELY SUSTAINED TYPE OF TEMPERATURE CURVE

In the third week, almost all moderate cases become steadily better The temperature becomes diurnal again and falls to normal within three or four days A

reduction in the pulse rate may accompany or precede it. The blood pressure begins to rise again and the fluid output exceeds the intake for several days. The rash has disappeared. The ulcer loses its scab and becomes a slightly depressed scar. There is some neural deafness. A coarse intention tremor of the hands is often present. The patient may be dizzy and too weak to walk the first time he tries. The sedimentation rate begins to rise. Retinal edema, if present, is maximal, as is the Proteus OX-K titer.

In the fourth week, most patients are afebrile. The sedimentation rate is at its highest, the pulse rate increases, coordinate with activity, and eosinophiles may appear in the blood for the first time since the onset of fever. The hemoglobin begins to rise. Leucocytosis (10,000 to 12,000) is common. In most cases the OX-K titer rapidly diminishes. The patient can walk about but develops neurocirculatory symptoms as soon as he exceeds his limited emotional and exertional tolerance. The pale scar of the ulcer may persist for a long time and the return of eye grounds, sedimentation rate and pulse to normal may require additional weeks.

Death in patients manifesting only the above symptoms and signs did not occur except in the case of massive intestinal hemorrhage, an unpredictable but rare disaster.

#### b. "Dangerous" scrub typhus

Although all cases looked much alike during the first week of illness, one or more groups of signs characteristic of a "severe" infection appeared in the second week or later in a minority of patients, varying in number with the severity of any given "epidemic." These were (1) excessively high fever, (2) severe tachypnoea with or without cyanosis, (3) meningismus, delirium, convulsions or coma, (4) marked cardiac enlargement and prolonged gallop rhythm, (5) massive albuminuria, severe oliguria, isosthenuria or uremia, (6) edema, ascites, marked hypochloremia, (7) jaundice, (8) multiple hemorrhagic phenomena.

The general characteristics of "dangerous" scrub typhus and the contrast between "severe" or "grave" illnesses and the "mild" or "moderate" disease described above can best be illustrated by the following gravely ill case (fig 5).

*Case report* Patient No 95, aged 22 years, was admitted 28 May, 1944, on the fourth day of fever, having been in strenuous jungle combat until his evacuation by air on that day. He had headache, cough, and pain in the eyes, but did not seem very ill. He had no eschar, but the diagnosis was established by lymph node enlargement, which progressed, by a typical rash (seventh to nineteenth day) and by the general course of the illness. The maximal Proteus OX-K titer was 1:100.

The *first week* passed uneventfully. The temperature did not exceed 102°, the pulse stayed below 90, and the respirations below 22 per minute.

During the *second week* the fever became much higher, reaching 104° or more regularly. Toward the end of the week the cough increased, the respiratory rate rose to 28 per minute, breath sounds were diminished at the bases, and a few rales were heard over the right lower lobe. The pulse rate increased to 100 per minute.



The first heart sound became soft, gallop rhythm developed, and slight cardiac enlargement was suspected. At about the same time a queer silent depression

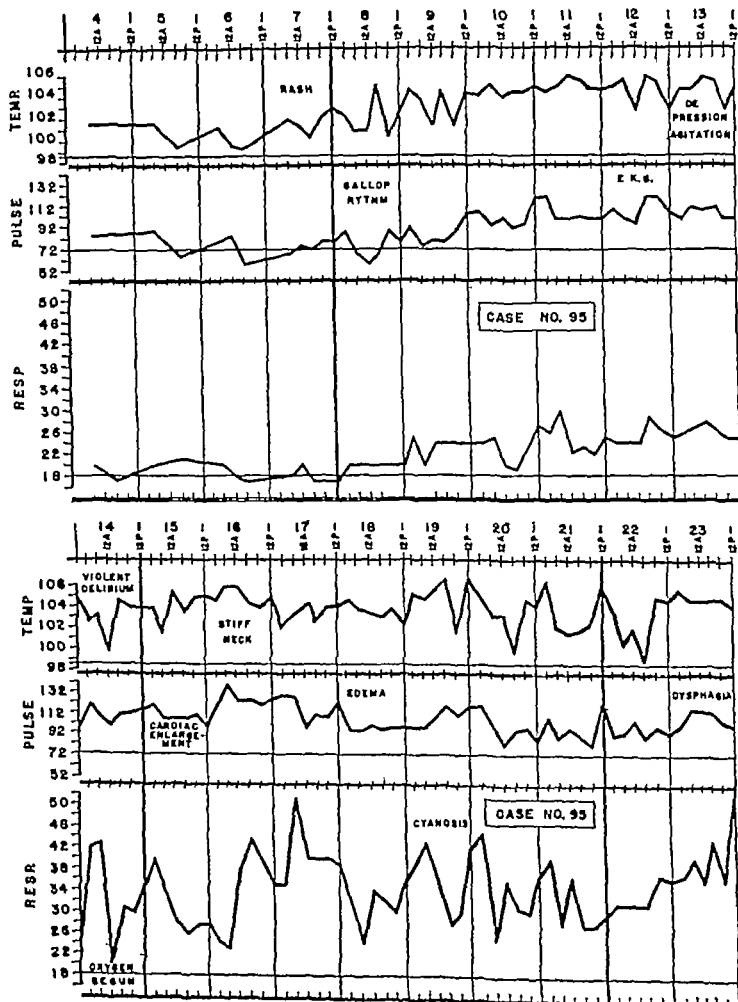


FIG 5 CASE #95 GRAVE SCRUB TYPHUS  
See case report in text

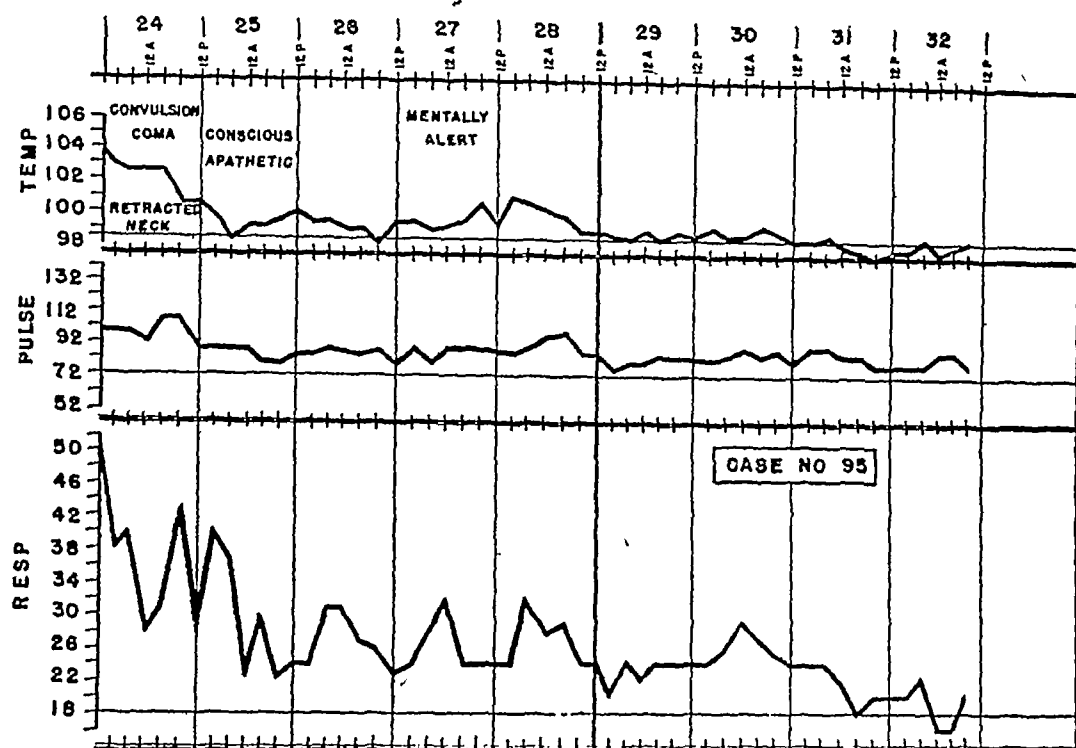


FIG 5 (Continued)

and agitation developed, myoclonic jerkings began, and restraints were necessary to keep the patient in bed. Retinal venous engorgement and mild retinal edema appeared. Appetite decreased. Fluids had to be given intravenously to maintain adequate intake. The patient was quite sick but did not appear to be in immediate danger.

During the *third week* the fever at first dropped slightly, but toward the end of the week began spiking to  $105^{\circ}$  with chills and sweats. The respirations rose to 42, without any increase in pulmonary physical signs. Slight cyanosis was detected and oxygen therapy was begun. Toward the end of the week, marked cyanosis appeared whenever oxygen was not administered. An X-ray of the chest showed slight mottling in the lower lobes. During the week, cardiac enlargement increased, the apex impulse being felt in the anterior axillary line. A double diastolic sound was heard at the apex. The pulse reached 140, and the blood pressure was 90/60. The electrocardiogram showed a small T wave but was otherwise not remarkable (fig 25k). Generalized edema appeared, but this was not thought to be due to cardiac failure because the veins and liver were not engorged and pulmonary congestive signs were absent. During this week rigidity of the neck appeared, without spinal fluid abnormality. Cheyne-Stokes respiration occurred. Combativeness and severe delirium made their appearance but subsided somewhat toward the end of the week. Retinal edema was marked, and subconjunctival hemorrhages were seen. The urine volume diminished, then the patient became incontinent. The blood urea nitrogen remained normal (16 mgm per cent). The hemoglobin had fallen to 9.6 gms.

In the *fourth week* no striking change occurred until the 26th day when the

patient had a convulsion. After this he was comatose for twelve hours. Toward the end of this week the serum proteins dropped to 4.6 gms per cent despite blood and plasma transfusions. The patient became almost unable to swallow and tube feedings were begun. At about this time the temperature declined steadily but he remained as sick as ever, emaciated, restless, jerky, confused, and cyanosed. He talked with a peculiar metallic stuttering voice. The systolic blood pressure remained about 90, the pulse rate dropped below 100, and the respirations declined to 36 per minute.

During the *fifth week* the patient was afebrile. The respiratory rate declined to 24. He began to look as if he might recover, but he was extremely thin, asthenic, apprehensive, querulous and tremulous. The blood pressure rose to 126/100. The retinal changes disappeared.

In the *sixth week* he began to eat. The blood pressure rose to 138/110. Cardiac enlargement was still apparent, and gallop rhythm was still audible. At this time the patient began to complain of painful, cold feet, and developed intense hyperesthesia of the toes and soles which tormented him for two weeks.

In the *seventh week* an electrocardiogram showed marked T-wave inversion (fig 25l) but the hypertension and cardiac enlargement were less marked. In the *ninth week* the cardiac size and blood pressure were normal. The patient was able to get out of bed for the first time since onset. From this point on, convalescence, though slow, was uneventful.

In the *sixteenth week* an electrocardiogram was normal (fig 25m). By the *eighteenth week* the patient had regained most of his lost weight and strength.

This patient, with extensive pulmonary, cardiac, central nervous system and probably renal involvement, was one of the sickest cases in our series who recovered.

### c *Mortal scrub typhus*

Of the patients with "dangerous" scrub typhus, half were classed as severely ill, one quarter were considered gravely ill, and the remainder died. Death was more often gradual than sudden. It occurred any time between the 9th and 28th day of illness but was mainly confined to the early third week (figs 20, 21). Mortal cases often did not differ much clinically from the gravely ill until the last few hours, when convulsions, pulmonary edema or unabolishable cyanosis supervened. From the bedside it appeared that the immediate cause of death was a combination of pneumonitis and encephalitis.

At autopsy, the impressive fact was not that a disease process in any one organ was responsible for death, but that overwhelming infection was present with extensive involvement of many organs and tissues. These included, in addition to those in which major dysfunction endangered life, the lymph nodes, the spleen, the skin, blood vessels and the testes. All fatal cases showed this extensive involvement, including two patients dying unexpectedly of convulsions and one who died on the 11th day of illness from a fulminating gastrointestinal hemorrhage without any other clinical signs of a severe infection.

The basic pathologic change seen under the microscope was acute inflammation

in interstitial tissue, with edema, areas of endothelial swelling, and a cellular infiltrate composed of histiocytes, lymphocytes and plasma cells. Perivascular tissues and the adventitia of vessels were widely involved, but endarteritis was not conspicuous and the thromboses and gangrene, common in other rickettsial infections, were rarely seen. A striking feature was that, in spite of the widespread acute nature of the pathologic process, few changes were seen which did not appear reversible and actual destruction of tissue rarely occurred.

#### 4 CLINICAL VARIATIONS, STATISTICS, AND LABORATORY FINDINGS CHARACTERISTIC OF SCRUB TYPHUS IN GENERAL

##### *a Incubation period*

This is usually stated to be from 7 to 18 days. Our experience has, in general, been compatible with such a figure but in only four instances have we found clear-cut evidence bearing on this point. Two medical officers who developed scrub typhus gave specific data concerning their incubation period and onset. One officer visited an endemic area, stayed for four days, and, six days after leaving, noted a papule (which later became a typical mite ulcer) on his antecubital fossa. Four days after this he developed fever. The second officer stayed four days in endemic areas, found a papule on his leg seven days after he left and developed fever two days later. These observations established incubation periods of between ten and fourteen, and nine and thirteen days respectively. Two other patients developed fever twelve and fourteen days after leaving focal areas, but the upper limits of their possible incubation periods were uncertain. The finding of ulcers by patients before the onset of symptoms was not uncommon and 25 of our patients had done so one to fourteen days before they recognized that they were ill.

##### *b Onset (figs 6, 21)*

Aside from the slightly painful or asymptomatic ulcer and the tender regional lymph nodes, prodromal symptoms were occasionally reported. They included headache, malaise, anorexia and weakness. Any other symptoms were accounted for by associated diseases. The fever was accompanied by headache, chilliness, anorexia, cough, listlessness, mild generalized aches and malaise. In 12 patients who developed scrub typhus while in the hospital for some other condition, there were no rigors before the third day. Those who became ill in the field sometimes stated that their illness began suddenly with a chill.

##### *c General symptomatology*

Pain occurred as in any febrile disease, but it was not a striking or outstanding feature of scrub typhus. The head, eyes, neck, back and abdomen were the most common sites. An occasional patient complained bitterly of a localized pain in the jaws, ears or tongue.

Chills occurred characteristically during the period of spiking fever. Drenching sweats usually followed them.

Nasal congestion was almost universally present. Sore throat was a common symptom. The findings in the pharynx were usually minimal. Cough was extremely common. It was often the most annoying symptom of the disease.

Anorexia was common and sometimes severe. Nausea and vomiting occurred but persistent vomiting was infrequent. When diarrhea appeared, it was usually due to intercurrent disease.

Cardiac pain did not occur. Palpitation was very rare during the acute phase. It was conspicuous in only one case.

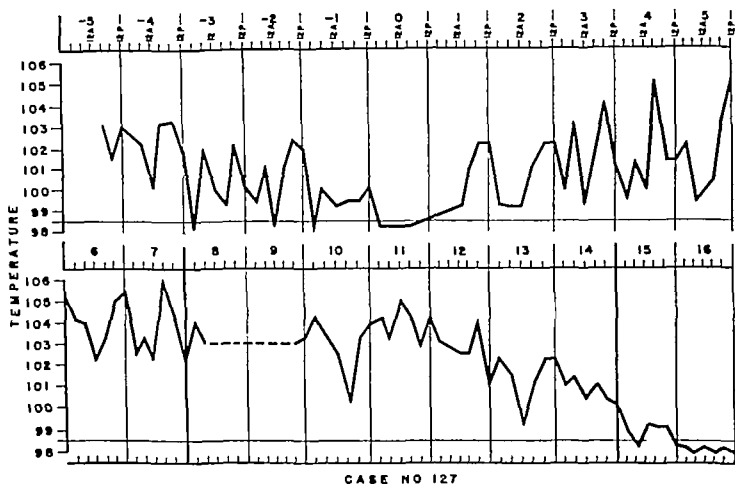


FIG. 6. SEVERE SCRUB TYPHUS PRECEDED BY BENIGN TERTIAN MALARIA.

The character of the onset is illustrated. Temperatures were not recorded during transportation of the patient from a forward installation to this hospital on the 8th and 9th days of fever.

The patients were apt to be apathetic, drowsy and to show nocturnal confusion. Some of them became apprehensive, hyperesthetic and querulous. Slight deafness was almost the rule.

#### d. Physical signs

(1) *Facies*. The patient's facial appearance has often been described as showing diagnostic characteristics. There is no doubt that these individuals have something about them which may give the experienced clinician a diagnostic clue: the marked flush, the dull red eyes, the periorbital edema, and the slightly open mouth, from nasal congestion (fig. 7). We believe, however, that the specificity of the facies has been overemphasized.

(2) *Ocular signs*. Major Harold G. Scheie (3) made a special study of the eyes of 451 patients. He examined them each week during the febrile course and followed them during convalescence until ocular abnormalities disappeared.

(a) External Conjunctival injection occurred in 38 per cent. It was present in the first week and tended to disappear in the second and third weeks. Subconjunctival hemorrhages appeared in 64 per cent, usually during the first ten days. Eighteen were bilateral, eleven were unilateral. They were often quite massive, at times covering one third to one half of the exposed sclera. Ecchymosis of the eyelids was seen in one per cent, early in the disease. Nystagmus of a peculiar type occurred in two patients. It consisted of coarse, irregular, jerky, incoordinate movements of the eyes from side to side while attempting to fix on an object.



a

b

FIG 7 THE FACIES OF SCRUB TYPHUS

a Case #350 "Typical" facies in a moderately ill patient on the 8th day of fever, showing periorbital and malar puffiness, open mouth from nasal congestion and apathetic countenance.

b Case #36. Facies of a patient (12th day of fever) who died suddenly after a convulsion on the 17th day.

(b) Internal Changes in the fundus. During the first or second week, the retinal veins became markedly engorged in 67 per cent of cases, frequently reaching a diameter two to two and a half times the size of the arteries. As the engorgement increased, the veins became tortuous and their outlines were blurred by what was thought to be a perivascular exudate. Venous thrombosis occurred in only one case. At arterio-venous crossings, the arteries seemed to indent the dilated veins. The arteries showed some blurring of outline, but less than the veins.

Edema of the disc and retina was noted in 36 per cent. It was always bilateral.

and was preceded by engorgement of the veins. The edema involved both the disc and the surrounding retina. Swelling of the disc was never marked, usually less than 1.5 and never over 2.5 diopters. This retinal edema was not related to increased spinal fluid pressure, it was not accompanied by changes in vision. Consequently, it was thought to represent a local inflammatory change, rather than optic neuritis or a true papilledema. It occurred with greater frequency in the severely and gravely ill cases.

Retinal hemorrhages occurred in 6.6 per cent, usually superficial and flame shaped, but occasionally deep and punctate. Retinal exudates occurred in 4.9 per cent, usually of the cotton wool type. When hemorrhages and exudates occurred, they appeared at the height of the retinal edema mentioned above.

Retinopathy of this type has not been seen in other febrile diseases in this area. Consequently, it was frequently helpful in diagnosis. Major Schiele made the diagnosis in several atypical cases a week before the agglutination reactions became positive. Retinopathy appeared from the 10th to the 17th day, and disappeared between the 5th and 8th weeks. Uveitis was seen in 1.3 per cent. Vitreous opacities were noted in 4.6 per cent. Both were usually asymptomatic and disappeared early in convalescence. Secondary glaucoma appeared in one case.

(3) *The primary lesion (figs 8 & 9)* Sixty per cent of our 200 patients had a primary ulcer, while in 40 per cent none was found despite careful search. The distribution is shown in figure 10. The usual characteristics are described under the "textbook picture". Many variations occurred. Lesions on moist intertriginous surfaces (axillae, scrotum, perianal region) appeared as shallow, yellow-based ulcers without much surrounding hyperemia and without the black crust, consequently they were easy to overlook. Lesions on the hands and those below the popliteal space were often indistinguishable from the many cutaneous erosions and leech bites sustained by troops traversing the jungle. An occasional patient insisted that he pulled a tick or a leech from a certain place on his skin where a typical "mite-bite" primary lesion developed subsequently. The vast majority of patients did not report feeling any "bite". Secondary infection was rare. Two patients had mild lymphangitis extending from the ulcer. Two patients had two primary ulcers and we have seen a case in another hospital with three. In some cases, a very shallow erosion healed in a few days and the presence of transient tender adenopathy and a residual scar or spot of pigment suggested that it was a true primary lesion. As demonstrated in Major Machella's series of Chinese patients, excision of the primary lesion did not affect the course of the disease. The presence or character of the ulcer appeared to have no relation to any other manifestation of the disease, including the OX-19 titer and the severity.

(4) *Lymphadenopathy* Thirty per cent of patients with ulcers (20 per cent of all cases) developed enlargement and tenderness of the regional lymph nodes. This was often noted before the onset of other symptoms. During the first few days of fever, all but six patients developed generalized lymphadenopathy. Frequently certain chains were spared, such as the epitrochlears and occipitals, but often all the main groups as well as certain unusual nodes in the axillar or pectoral

regions could be felt. The most dependable were the axillary lymph nodes, which rarely failed to be palpable. The least dependable were the inguino-femoral

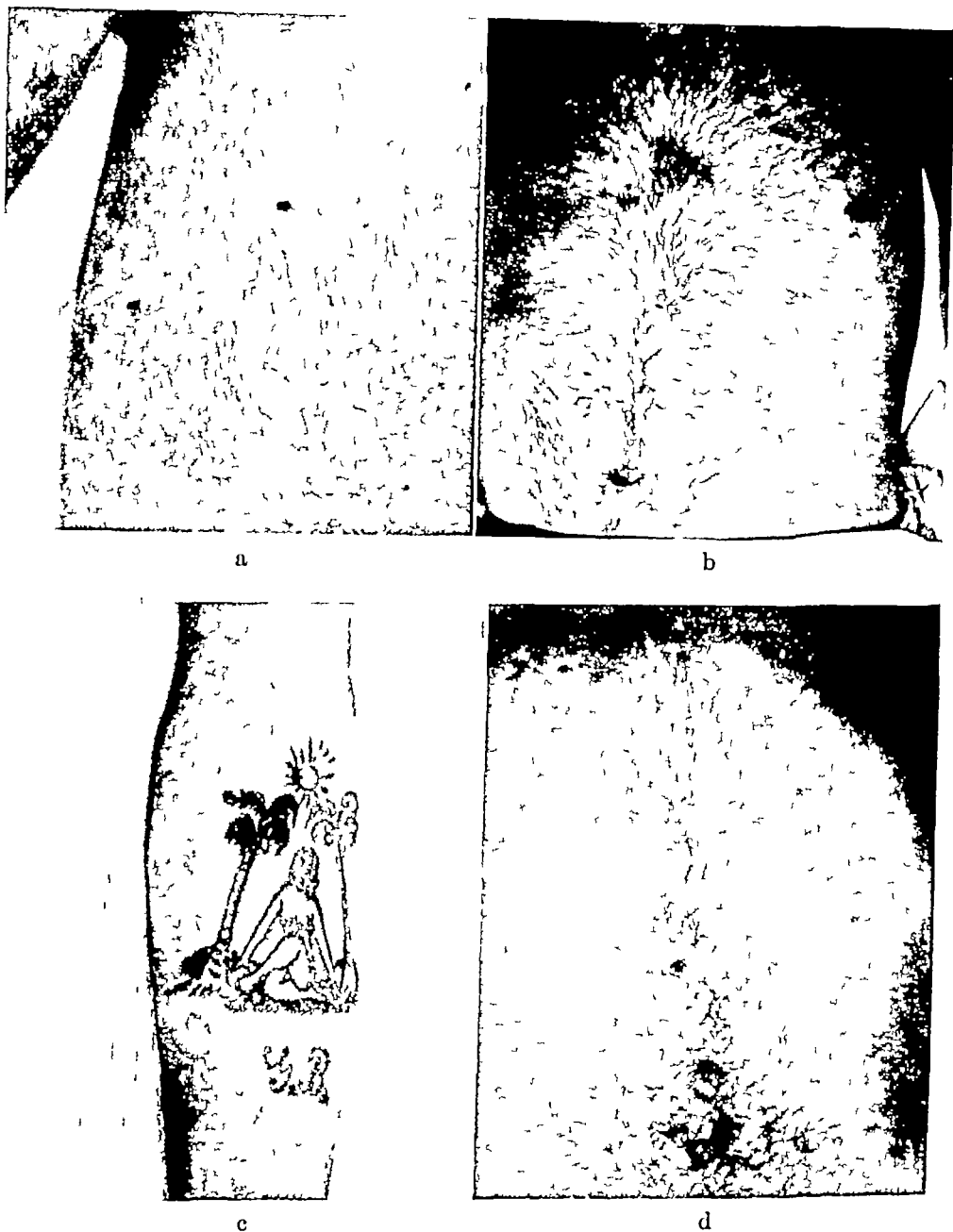


FIG 8 THE PRIMARY LESION

- a Case #45 Posterior thigh lesion about the eighth febrile day
- b Case #51 Thoracic lesion with crust and areola, sixth day of fever
- c Case #17 Fore arm lesion with crust and desquamation. Fourteenth febrile day
- d Case #39 Abdominal wall lesion with crust and beginning desquamation, about the tenth day of fever. The rash is also shown

nodes, which were so regularly enlarged from other causes in troops operating in the jungle. The nodes were usually large and rubbery but were at times small



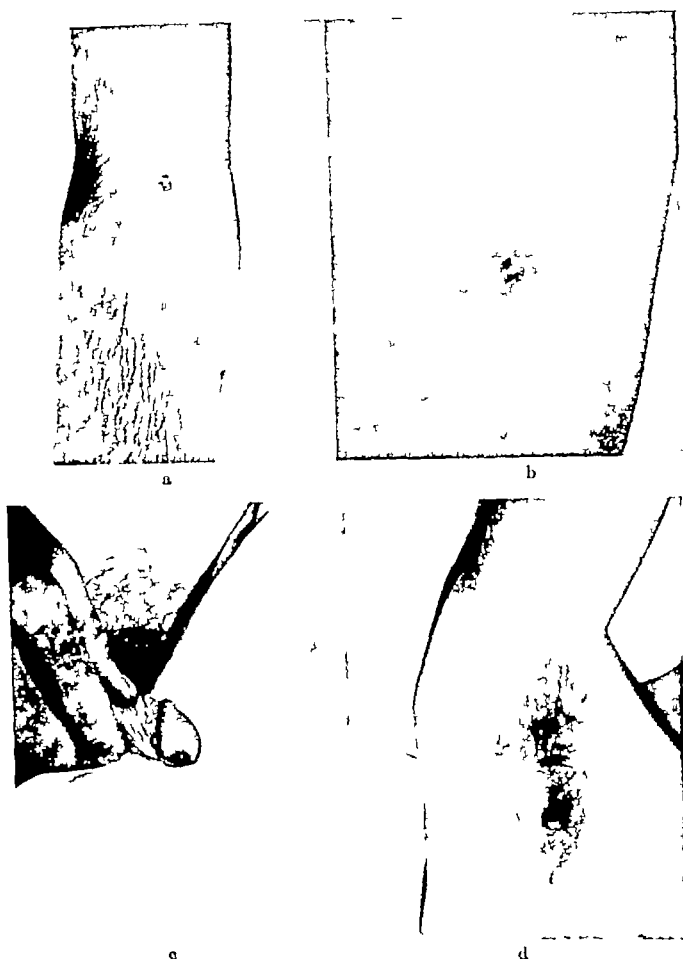


FIG 9 OTHER ASPECTS OF THE PRIMARY LESION

- a Case #47 Posterior thorax lesion beginning to heal on the fourteenth day of fever
- b Case #51 Antecubital lesion with crust removed, showing weeping ulcer crater and raised edges Eighth febrile day
- c Case #35 Penile lesion The rash can be seen on the fingers
- d Case #41 Axillary lesion a shallow erosion without a crust

and firm. They were always discrete, and usually moderately tender. The nodes draining the primary ulcer were usually larger than the rest and more

tender Lymph node biopsies were done in a number of patients in Major Machella's series. The nodes were pinkish-red, sometimes hemorrhagic, and swollen with edema fluid. A few showed small yellowish spots of early necrosis. At autopsy, the nodes in the mesentery, retroperitoneal region and mediastinum were enlarged to an equal or greater degree than the superficial chains.

(5) *The rash (see fig 11)* A rash occurred in 71 per cent of cases. It appeared from the third to the seventh day of fever, most commonly the fifth. It was usually maximal between the sixth and ninth day. An appreciable number of patients had a rash of only 24 to 48 hours' duration, but the majority lasted four to nine days and a few as long as ten to fourteen days, occasionally outlasting the fever.

The eruption was most often coarse and maculopapular. It involved the trunk always and the extremities in about a third of the patients. The face was in-

11% <i>Upper extremities</i>		13% <i>Pudendal region</i>	
Supraclavicular	3	Penile	2
Shoulder	4	Scrotal	8
Arm	2	Perianal	1
Antecubital fossa	3	Gluteal	4
Knuckle	1		
17% <i>Axilla</i>		27% <i>Lower extremities</i>	
		Thigh	12
		Popliteal space	5
		Calf	7
29% <i>Trunk</i>		Ankle	8
Thorax	11	Heel	1
Abdominal wall	2		
Umbilicus	5	3% <i>Other</i>	
Flanks	9	Neck	3
Inguinal	5	Eye lid	1
Sacral	3		

FIG 10 DISTRIBUTION OF 120 PRIMARY LESIONS

involved in 15 per cent. A clear-cut rash was not seen on the palms or the soles. A florid rash was seen in eight per cent. In 35 per cent it was purpuric. Rarely it consisted of only a few scattered macules. There was no correlation between the appearance, character or persistence of the rash and the severity of the disease. The rash was often difficult to see in the early stages, especially in Chinese. Cross lighting was helpful in such cases.

(6) *The fever* We came to look upon an irregular spiking type of temperature chart with double daily rises as characteristic of scrub typhus (figs 3, 12). Statistical study of our cases showed that 70 per cent of patients had this type of fever curve at some time during their course. However, it did not as a rule persist throughout, giving way in many to long or short periods of remittent or sustained fever (fig 4). Complications always accounted for recrudescence of pyrexia, once the normal line had been reached and maintained for 24 hours. However, Major Machella reported definite relapses in two Chinese patients (2).

(7) *The pulse* Ninety five per cent of patients had a pulse rate of over 100 per minute at some time during their course In mild and moderate cases, the pulse



FIG 11 THE RASH

- a Case #220 Sparse maculopapular rash on the fifth febrile day
- b Case #42 Fine discrete rash, largely macular on the sixth day of fever
- c Case #77 Well developed maculopapular rash on the 8th febrile day
- d Case #85 Blotchy coarse maculopapular rash on the 10th day of fever

rate tended to be relatively slow in relation to the degree of fever The sharp spikes of the temperature chart were reflected to some extent in the pulse rate

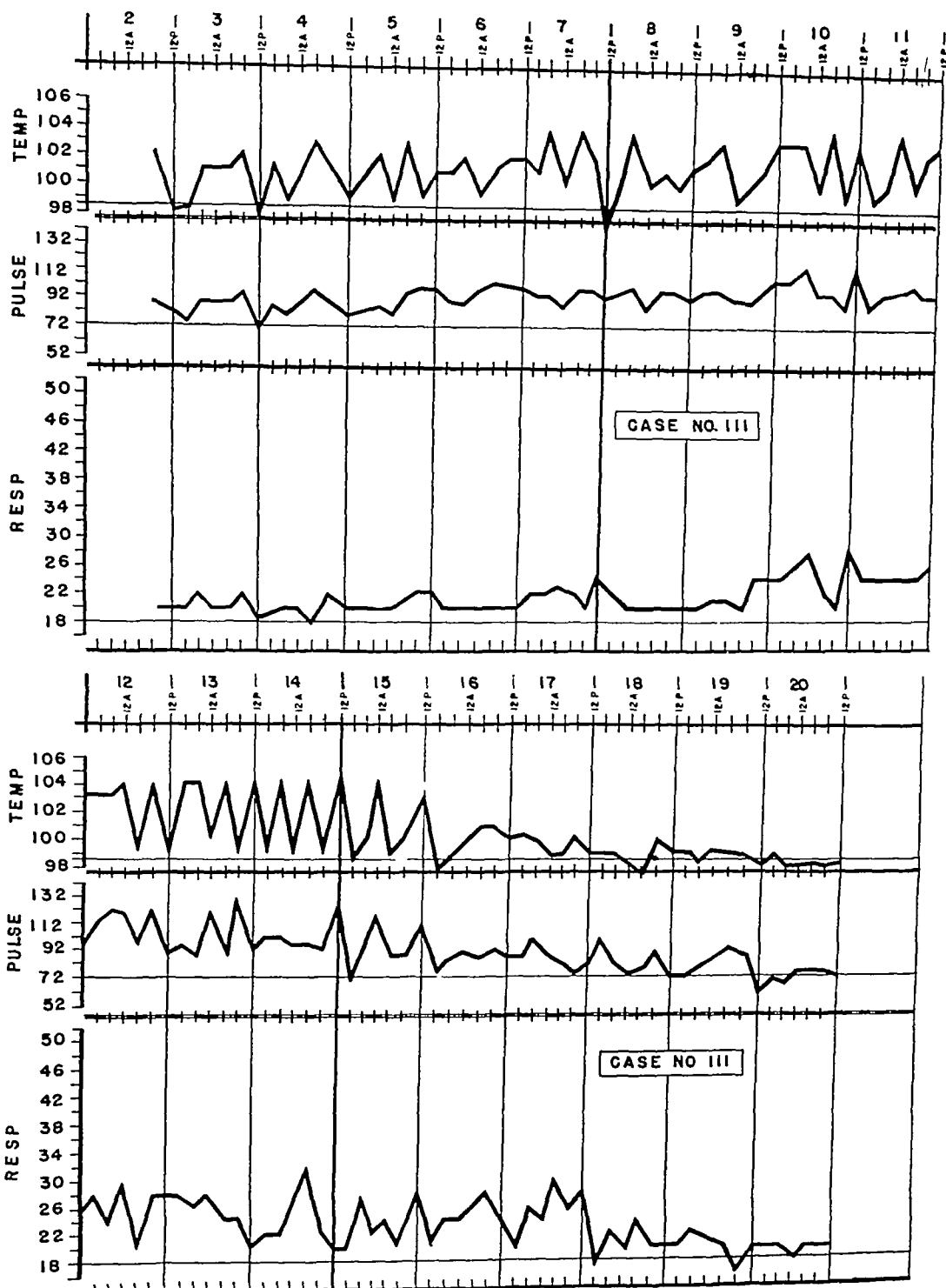


FIG 12 CASE III SEVERE SCRUB TYPHUS WITH AN UNUSUALLY PERSISTENT PATTERN OF DOUBLE DAILY TEMPERATURE SPIKES

Rates of 120 rarely were exceeded in moderate cases and never in patients whose disease was mild. Even in the severely ill, elevations above 130 per minute were brief and not common. Gravely ill and mortal cases sometimes had marked

tachycardia. Not infrequently the pulse did not rise for several days after the onset of fever and fell to normal before defervescence was complete

(8) *The blood pressure* A daily record of blood pressure was not made in the majority of cases in this series. Major Machella studied this feature carefully in his group of Chinese patients. The blood pressure in the American patients did not drop to the low levels or remain low as long as it did in the Chinese, probably because the normal Chinese blood pressure is somewhat lower than the American. It began to fall gradually in the second week, usually reached its lowest level in the third week and then began to rise slowly. The lowest level recorded, except in pre-terminal shock, was 70/40. It occurred in a patient with a mild illness and persisted for several days. Moderate hypertension was seen twice during convalescence of grave cases. These are discussed in the Renal Section. The blood pressure level seemed to have no relation to severity or mortality. Frequent determinations were not found to be of practical use in the management of the great majority of cases.

(9) *The liver* This organ was often soft and difficult to palpate. It was slightly to moderately enlarged in 20 per cent of patients and was tender in 12.5 per cent.

(10) *The spleen* In 35 per cent of cases, the spleen was palpable. It was tender in 7.5 per cent. It was enlarged, soft and friable in all cases at necropsy and averaged 500 gms. in weight.

(11) *The respiration*<sup>1</sup> Most cases had a transient slight or moderate elevation of respiratory rate (24 to 30 per minute) which did not always correspond to the fastigium of the fever (see fig. 12). If tachypnoea was present, the diurnal respiratory rates tended to reflect the temperature spikes. Very few patients had an unvaryingly normal respiratory rate.

(12) *The lungs*<sup>1</sup> Most patients showed rhonchi, localized (usually basal) rales which often tended to change position from time to time, and areas of suppression or, occasionally, exaggeration of breath sounds. A few had dullness or impairment of the percussion note. Although these signs increased in frequency with severity of disease, they did appear in a considerable proportion of the "mild" and "moderate" cases (fig. 22).

(13) *The heart*<sup>1</sup> Soft first heart sounds were recorded in 33 per cent. Systolic basal or apical murmurs were heard frequently. These phenomena bore no statistical relation to severity of disease. Brief periods of gallop rhythm were common.

### c *Duration of the acute illness (fig. 13)*

In the statistical series the fever lasted from 10 to 36 days. In one subsequent case, the fever lasted only five days (fig. 14). In general, the duration of fever

<sup>1</sup> The minor cardiac and respiratory signs observed in scrub typhus were detailed above because they might occur in cases of any grade of severity without evidencing prognostically important degrees of involvement of the heart or the lungs. The phenomena seen in "dangerous" scrub typhus will be discussed in a subsequent section.

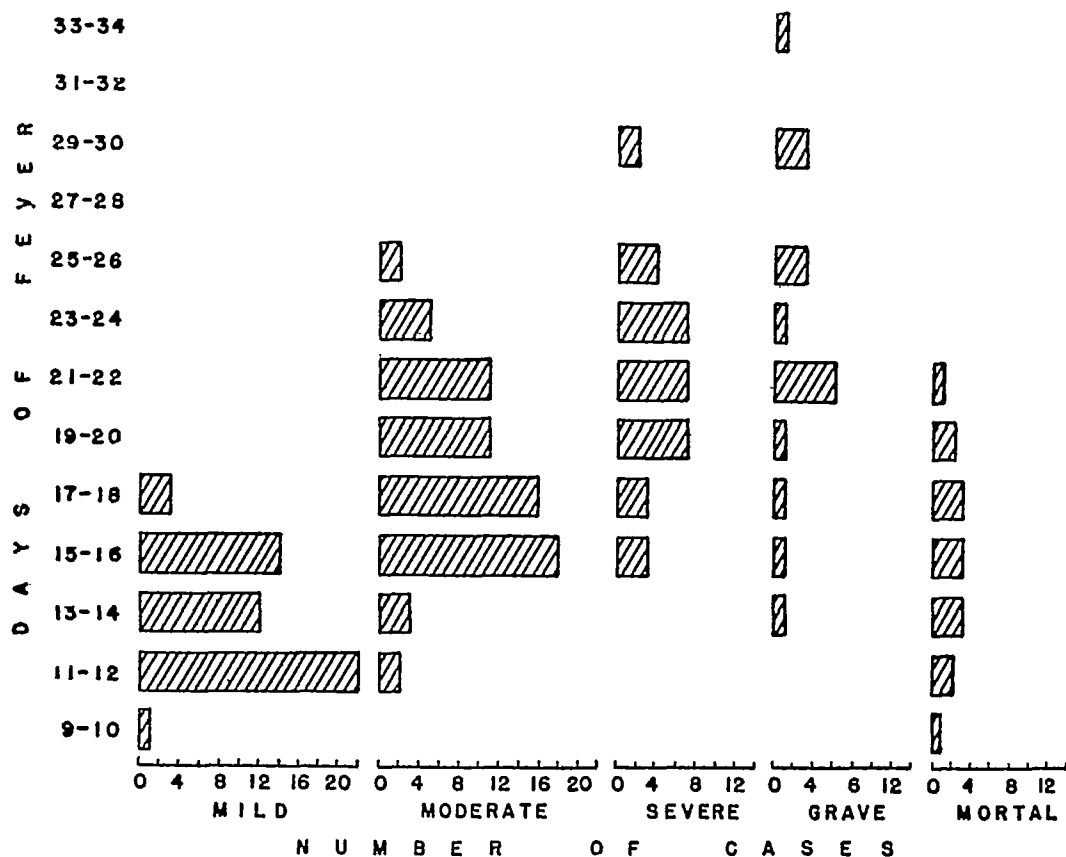


FIG 13 DURATION OF FEVER IN THE STATISTICAL SERIES OF 200 CASES  
Absolute figures are given

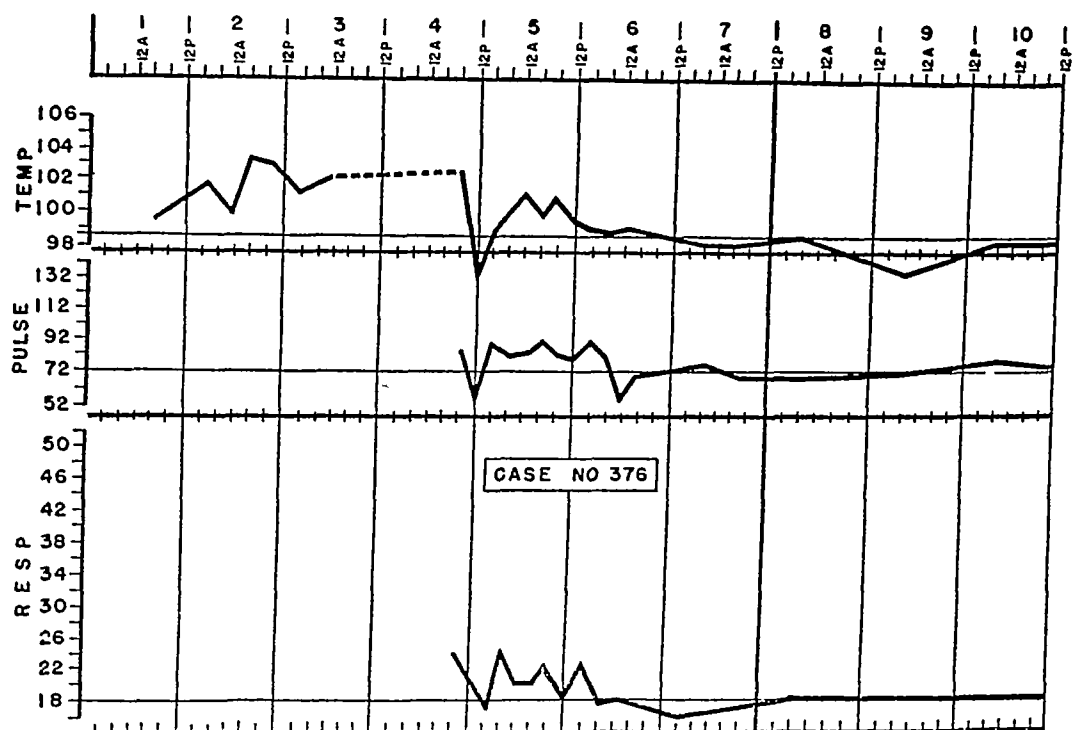


FIG 14 CASE #376 MILD SCRUB TYPHUS ENTIRE COURSE

Fever developed while in a forward installation for an unrelated condition. The temperature was not recorded during transportation to this hospital on the 3rd and 4th febrile days. This patient had a typical primary lesion, rash and lymph gland enlargement. The Proteus OX-K titer rose to 1 800 during the 3rd week after onset of the five-day fever.

was related to severity. However, several patients with protracted low fever were not severely ill, and two gravely ill patients had high fever of relatively short duration (fig 15)

*f Diagnostic laboratory findings and variations*

(1) *Hemoglobin* The hemoglobin tended to fall slightly during the first two weeks, the average reduction being 2.5 gms. In the grave cases, the period of falling hemoglobin was longer, and the degree of fall was greater, although these facts were somewhat masked by frequent transfusions. In some cases the hemoglobin dropped 25 per cent from the original level. The hemoglobin level began

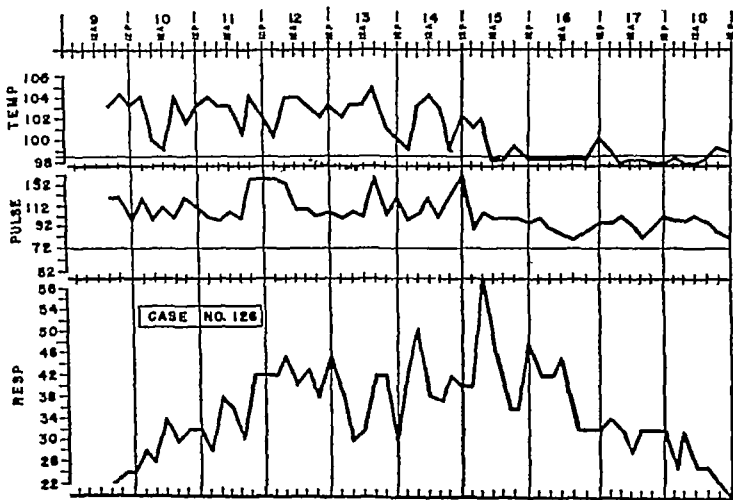


FIG 15 CASE #126 GRAVE SCRUB TYPHUS WITH "TYPHUS PNEUMONIA"  
The persistence of tachypnoea after the subsidence of fever is illustrated

to rise slowly at about the time of defervescence, and did not as a rule reach normal before the eighth week. These phenomena are shown in figure 16.

(2) *Leucocytes* (fig 17) The average total leucocyte count for 200 cases showed a slight rise during the second week, and a more definite rise after the fourth week. Individual cases sometimes showed considerable variation from these mean figures. A few had early leucopenias and a somewhat larger number had considerable leucocytosis, sometimes as high as 20,000 in the second or third weeks.

*Polymorphonuclear neutrophiles* increased during the second week, accounting for part of the rise in total count. After the tenth day, the absolute *lymphocyte* count, which had been slightly below normal, began to rise in all survivors. In gravely ill patients, this rise tended to be delayed until the fourth week. In most

of the mortal cases, it was slight or absent and lymphopenia frequently increased until exitus

*Monocytes* showed no striking changes

*Eosinophiles* were rarely seen after the first few days of fever. They reappeared with defervescence. Marked eosinophilias thereafter were usually due to hook-

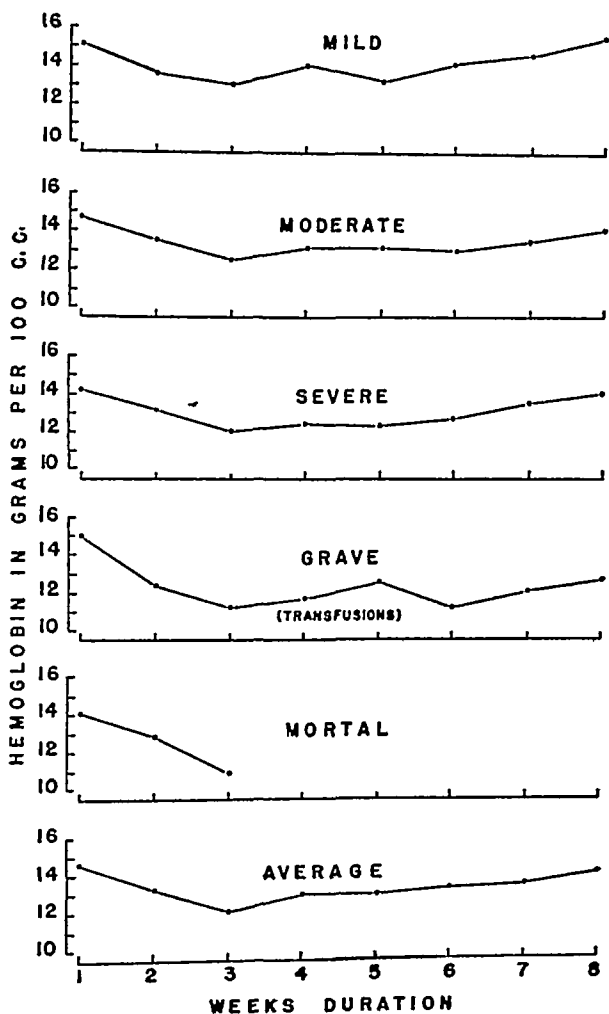


FIG 16 AVERAGE HEMOGLOBIN LEVELS FOR THE 200 CASES IN THE STATISTICAL SERIES, BASED ON 1000 DETERMINATIONS

The "grave" group received an average of 800 c cm of whole blood per patient during the period indicated

worm infestation which was so common in our patients as to make impossible an adequate evaluation of the scrub typhus blood picture during late convalescence

(3) *Weil-Felix reaction* The strain of B *Proteus* OX-K used in this hospital was supplied by the Army Medical School, Washington, D C. There was no significant rise in the titer of our patients' sera before the tenth day of fever. Many cases had titers of 1:100 or higher by the 14th day. The maximal titer



was reached in the fourth week in most cases, in the third week in some. After the 28th day, the titer almost always fell gradually and rarely remained significantly elevated after the eighth week. An occasional patient had a significant titer very briefly with a rapid fall thereafter, while a few maintained high titers for as long as we followed their sera—up to ten weeks at least. Titers of 1:25 were seen frequently and 1:50, occasionally, in patients with no history of a re-

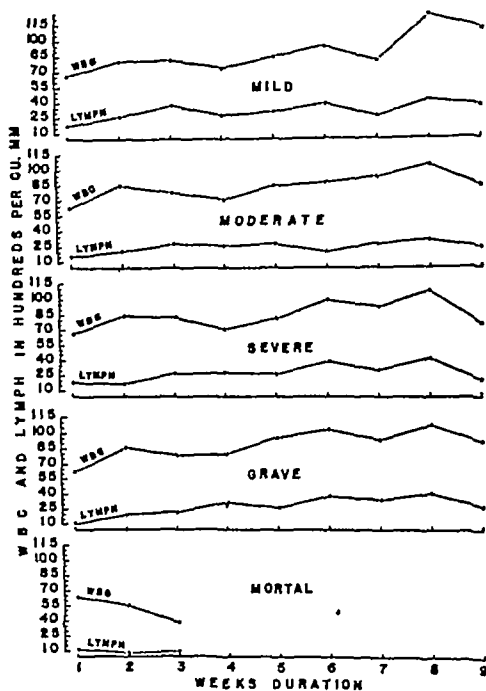


FIG 17 TOTAL WHITE BLOOD CELLS AND ABSOLUTE LYMPHOCYTE COUNTS ON THE 200 CASES IN THE STATISTICAL SERIES, BASED ON WEEKLY AVERAGES OF 1200 DETERMINATIONS

cent febrile disease. Titers of 1:100 or above were not seen except in scrub typhus. This level was therefore considered "diagnostic" in our series. The maximal titers obtained in 200 cases are shown in figure 18. Almost half of the series failed to have "diagnostic" titers. There was no relation of OX-K titer to disease severity, except that moderate cases appeared to have a somewhat higher proportion of significant titers. Low titers for OX-2 and OX-19, never in

over 1/50 dilution, occurred not infrequently, usually only in the first two weeks of disease and sometimes preceding the OX-K rise

The Weil-Felix reaction was occasionally of great value in the diagnosis of isolated atypical cases of scrub typhus and in differentiating with certainty between this and other types of typhus, as well as typhoid fever. In "epidemics", a clinical diagnosis was usually made before a significant agglutination titer developed. The 10th, 14th, 21st, and 28th days of disease were the times at which OX-K agglutinations were most helpful.

(4) *False positive Kahn reactions* Strong false positive Kahn reactions were seen in six cases. In two of these, extensive studies ruled out other known causes. Some persisted for many weeks after defervescence. All ultimately became negative.

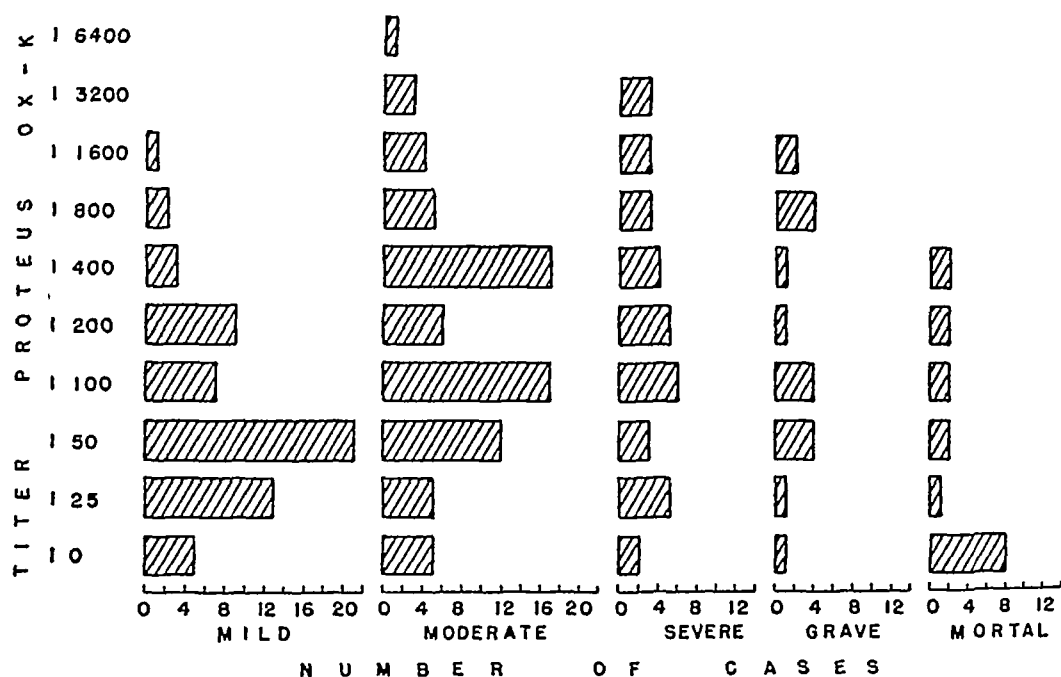


FIG 18 MAXIMAL PROTEUS OX-K TITERS IN 200 CASES IN THE STATISTICAL SERIES, SHOWING THE LACK OF ANY CLEAR-CUT RELATIONSHIP TO DISEASE SEVERITY

(5) *Sedimentation rate* There was a rough correlation between the degree of maximum elevation of the erythrocyte sedimentation rate and disease severity, as shown in figure 19. Often the elevation did not begin until defervescence was established and it persisted sometimes for two afebrile months, the most rapid rates being slowest to return to normal.

#### g Diagnosis

(1) In the absence of a full-blown clinical picture, the most helpful diagnostic clue was a careful history of the patient's location between one and three weeks before the onset of fever. The base areas around Ledo and Margherita in Assam were relatively safe. Beyond Ledo, anyone who had been off the Stillwell Road was a candidate for scrub typhus.

(2) Before the appearance of the rash on the third to seventh day, the only way of making a definite clinical diagnosis was by finding a typical primary lesion. It was essential to strip every suspected patient completely and to search the scalp, ears, eyelids, axillae, perianal area and genitalia in addition to the more easily inspected body surfaces. The primary lesion might or might not have a black crust, depending on whether it was located on a dry or moist surface. Its most significant characteristics were that it had a surrounding red flare, and that when fully developed it was usually "punched out" in appearance. The primary lesion, together with regional tender lymphadenopathy, was the earliest and most dependable of diagnostic signs.

(3) Increasing, generalized, usually tender lymphadenopathy was a valuable clue, although it could be mimicked by serum sickness, dengue, Weil's disease, secondary syphilis, infectious mononucleosis and sometimes other varieties of

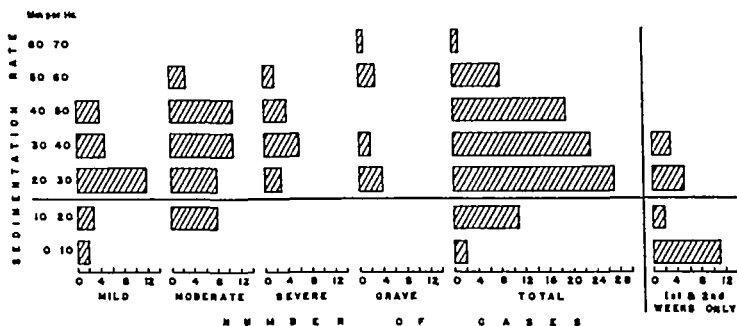


FIG 19 MAXIMUM ERYTHROCYTE SEDIMENTATION RATES OF 100 CASES OF SCRUB TYPHUS. The figures are higher in severer cases. The relatively low rates found during the first two weeks of fever are also shown. The maximum rate usually was reached in the third, fourth or fifth week after onset.

typhus. It was the most constant of the main diagnostic clinical signs, only three per cent of patients failing to manifest it in some degree.

(4) The rash was usually diagnostic when it was florid or typical. However, this was the case in only half the patients. It was sometimes difficult to differentiate from measles, and occasionally from drug eruptions and secondary syphilis. A petechial rash involving the palms and soles was not seen in scrub typhus.

(5) Other signs occasionally helpful in the first ten days of illness were subconjunctival hemorrhages, nuchal pain and stiffness, aching eyeballs and conjunctivitis.

(6) A leucocytosis during the first week tended to rule out scrub typhus. Thereafter, the leucocyte count was of relatively little diagnostic value.

(7) During the latter part of the second week, venous engorgement and edema of the retina sometimes gave a helpful diagnostic clue, since other febrile diseases in this area were not accompanied by such ophthalmic phenomena.

(8) At about the same time, the Proteus OX-K titer rose to a significant level in 50 per cent of our cases

(9) During the second or third weeks, a febrile patient with none of the above characteristics was suspected of having scrub typhus if he developed evidences of multiple parenchymal organ dysfunction, especially persistent muscular twitchings and marked tachypnoea with relatively few signs of pulmonary consolidation

(10) In our experience, the only conditions which it was mandatory to differentiate promptly from scrub typhus were cerebral malaria, bacterial pneumonia, meningococcal meningitis and, in surgical patients, sepsis. Since specific therapy could be given for these conditions without harm to the patient we usually eliminated them by a therapeutic test when any doubt existed. An early blood culture was taken to help rule out typhoid fever and plague, since infectious precautions were unnecessary for scrub typhus itself

## 5 CLINICOPATHOLOGIC CHARACTERISTICS AND DIAGNOSTIC CRITERIA OF THE MANIFESTATIONS OF "DANGEROUS" SCRUB TYPHUS

The general clinical picture of "dangerous" scrub typhus has already been outlined. It has been emphasized that such cases are clinically differentiable from mild and moderate cases by the occurrence of excessive amounts of fever, by the appearance of signs and symptoms of major organ dysfunction, or both—the result being a degree of illness and prostration which carried a high mortality.

In the following section, there is an analysis of the main phenomena of "dangerous" infection by systems. These phenomena are correlated with pathologic changes found by roentgenologic, electrocardiographic, chemical and postmortem examination.

### a *Pulmonary phenomena*

(1) *Pathologic findings:* In the statistical group, there were 17 deaths. At autopsy characteristic inflammatory lesions of the lung were demonstrated in all, though there was marked variation in the intensity and extent of the changes found. Characteristically, the lungs were boggy, bloody, firm and relatively airless, with a rubbery consistency rather than firm consolidation. Usually, the apices were spared. Roughly 75 per cent of lung tissue was involved in seven cases, 50 per cent in five, and 25–35 per cent in three. In the other two cases, the extent of involvement was not recorded quantitatively. In four autopsies on patients not included in the statistical group, these gross changes were wholly absent, the lungs showing only small patches of atelectasis or numerous tiny nodules of increased firmness and dusky color in relatively normal lung.

Microscopically, the minimal lesion uniformly present was an interstitial inflammation with alveolar walls moderately to markedly thickened due to vascular congestion and cellular infiltration by lymphocytes, monocytes and histiocytes, and with prominence and desquamation of alveolar epithelium. In more advanced lesions, small intra-alveolar hemorrhages occurred, moreover, edema fluid and inflammatory cells were seen in the alveolar spaces. In areas of lung showing marked gross changes, patches of basal bronchopneumonia, with areas of

fibrinous and polymorphonuclear exudate, were often seen, superimposed on the interstitial pneumonitis. This change, however, never monopolized the histologic picture. The uniformly occurring interstitial lesion appeared to be the primary pulmonary manifestation. The occasional polymorphonuclear bronchopneumonia was thought to be a secondary process.

(2) *The clinical pulmonary picture* During the second week of many cases of scrub typhus, thought to be only moderately severe, the patients became dyspnoeic as a result of the slight exertion of turning in bed, eating, talking or emotional disturbance. A few rales sometimes appeared at the lung bases, perhaps with diminution of breath sounds. A day or two later the respiratory rate began to spike to 36 or more per minute when the fever was highest (figs 5, 15). After this, a sustained tachypnoea developed and the patients became clinically much sicker. Later, they became dusky, then cyanosed without oxygen, then cyanosed in spite of oxygen. The longer this picture persisted, the greater was the frequency of respiratory death, usually with sudden pulmonary edema, after a convulsion, frequently in coma. A few patients developed a remarkable hyperpnoea—long, labored thoracic movements not associated with great subjective dyspnoea or orthopnoea, nor with cardiac failure nor acidosis. This hyperpnoea was not affected by oxygen therapy.

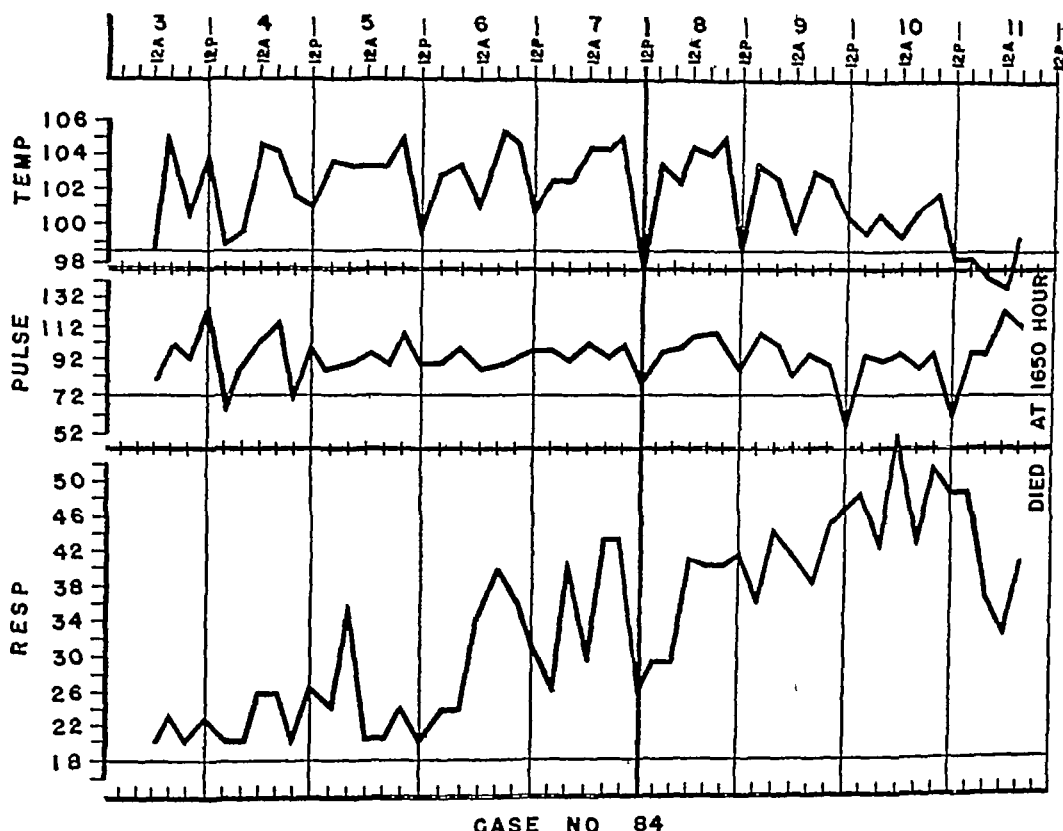
At any point in the course described above, unless unabolishable cyanosis or persistent hyperpnoea had supervened, recovery could begin. The "resolution" of the process appeared to be very gradual and the respirations remained elevated for many days, sometimes well after the subsidence of fever (figs 5, 15). Rarely a patient died a respiratory death after his temperature had reached the normal line (fig 20).

Typical signs of bronchopneumonic consolidation—crepitant rales, marked percussion impairment, whispered pectoriloquy, etc—were never found on examination of the chest. Patches of slight percussion dullness and crackling rales occasionally occurred but clinical diagnoses of bronchopneumonia based on these findings were often not confirmed at necropsy. Pyogenic organisms were uncommon in the sputum. No striking beneficial effects ever followed the use of the sulfonamides or penicillin, moreover, bronchopneumonic consolidation was seen at autopsy as frequently in patients treated with these chemotherapeutic agents as in those who did not receive them. Patients who survived the longest were more likely to have purulent sputum and basal bronchopneumonic patches at autopsy but the clinical and pathologic picture of rickettsial pneumonia was always basic.

(3) *Röntgenographic pulmonary findings* Prominent hilar and trunkal markings were frequently reported at all stages of the disease. The markings in the peripheral lung fields were sometimes exaggerated. Some patients had localized densities resembling patchy bronchopneumonia or lobular atelectasis but the autopsy did not always confirm such X ray diagnoses. Rarely, a diffuse haze or "ground glass" appearance of the lung fields was seen. In some cases, diaphragmatic excursion was reduced, occasionally to a marked degree.

The roentgenographic picture of the scrub typhus chest often seemed to bear

little relation to the clinical evidences of respiratory dysfunction. Roentgenograms taken within three days of death might or might not show marked abnormality. One patient who had a film taken 36 hours before he died showed only the prominent hilar and trunkal markings interpreted as "tracheobronchitis." Yet, he had clinical signs of extensive pulmonary involvement (marked tachypnoea and progressive cyanosis) at the time the film was made, and at autopsy 80 per cent of his lungs were involved by severe interstitial pneumonia.



CASE NO 84  
FIG 20 CASE #84 MORTAL SCRUB TYPHUS

The fever appeared to be subsiding when death occurred in association with clinical signs of "typhus pneumonia", meningoencephalitis, myocarditis and anuria. The exact date of onset of fever being unknown, the days since the patient's original hospitalization are given instead.

(4) *Diagnosis and prognostic significance of "scrub typhus pneumonia"* (the following statements are based on an analysis of 139 consecutive cases with 17 autopsies).

(a) The most dependable sign of clinically important "scrub typhus pneumonia" was cyanosis of the skin which at first was dramatically relievable by high concentrations of oxygen. Cyanosis confined to the fingernails was not of significance, it occurred in many febrile patients who were not thought to have a major pulmonary lesion. Whenever general cyanosis was present, extensive rickettsial pneumonia was almost certainly present. However, cyanosis was absent except terminally in two individuals who, at autopsy, were found to have

75 per cent of the lung involved. Consequently, it was useful mainly as a positive sign, its absence was not a reliable indication of the absence of extensive pulmonary involvement. The prognostic importance of cyanosis is illustrated by the following figures:

	Mortality
All cases requiring oxygen	36 per cent
Cyanosis for two days	38 per cent
Cyanosis for five days	56 per cent
Cyanosis unrelieved by oxygen	100 per cent

(b) The respiratory rate chart proved to be the most sensitive indicator of the presence of "scrub typhus pneumonia." An analysis of the relationship of tachypnoea to severity of illness is given in figure 22.

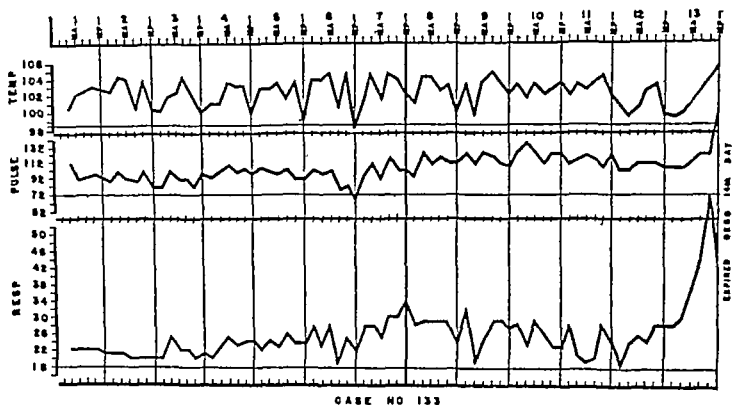


FIG 21 CASE #133 MORTAL SCRUB TYPHUS ENTIRE COURSE

This patient was admitted for a minor urological complaint before the onset of systemic symptoms. The minimal degree of tachypnoea (prior to the terminal rise) is noteworthy. Extensive interstitial pneumonitis was found at necropsy.

The frequency of slight respiratory rate elevations not exceeding 24-30 per minute for a few days has already been noted as a characteristic of almost all scrub typhus cases. Even such slight tachypnoeas were so definite and so frequently associated with minimal physical signs of parenchymal lung disease that they were thought to reflect at least a small pulmonary lesion in the majority of cases. However, since no patient died or was gravely ill whose respiratory rate remained under 32 per minute, we felt that slight tachypnoeas did not reflect a prognostically important amount of "typhus pneumonia."

Rates between 32 and 35 per minute for two days justified concern because, although they could occasionally occur in mild illnesses, a small number of patients who died with 25 per cent of their lungs involved by rickettsial pneumonitis had no more tachypnoea than this during life (fig. 21).

When the respiratory rate reached 36 or more per minute on two days, the statistical mortality rose to that of the "dangerous" group as a whole and few patients failed to become severely ill. Longer periods of tachypnoea and very rapid rates were associated with a high mortality and all such patients who came to necropsy had massive lung lesions.

Tachypnoea was generally more useful as a prognostic sign than cyanosis because it occurred more frequently, usually appeared earlier, and because, as figure 22 shows, only 60 per cent of fatal cases were cyanosed except pretermi-

RESPIRATORY RATES	SEVERITY GROUPS				
	Mild (39)	Moderate (40)	Severe (26)	Grave (17)	Mortal (17)
Less than 32/minute	90%	67%	30%	0	0
32-35/min for 2 days	10%	13%	8%	12%	12%
36/min for 2 days	0	7%	20%	11%	20%
36/min for three days	0	13%	27%	59%	20%
36/min for 7 days	0	0	15%	18%	48%
Cyanosis	0	0	20%	41%	60%
Physical signs (exclusive of rhonchi)	28%	65%	92%	100%	76%

FIG 22 FREQUENCY OF RESPIRATORY RATE ELEVATION IN 139 CONSECUTIVE SCRUB TYPHUS PATIENTS

Figures given are percentages of the number of cases in each severity group. The frequencies of cyanosis and physical signs (fine rales, altered breath sounds or dullness to percussion) are given for comparison.

nally. The relationship of various degrees of tachypnoea to mortality may be summarized as follows:

	Mortality
Respiratory rate less than 32 per minute	0 per cent
Respiratory rate 32 to 35 for 2 days	13 per cent
Respiratory rate 36 per min. for 2 days	23 per cent
Respiratory rate 36 to 50 for 7 days	50 per cent
Respiratory rate 50 per min. for 2 days	80 per cent

(c) Physical signs in the chest. Less reliable diagnostically and prognostically than the respiratory rate were the physical findings in the lungs themselves. Persistent fine, moist, basal rales, often with some reduction of breath sounds and impairment to percussion, were found in 10 of the 17 patients who died. When these signs appeared, they usually failed to indicate the extent of the pulmonary lesion. Moreover, some cases with extensive "typhus pneumonia" had no physical signs to indicate its presence. In some patients without tachypnoea or cyanosis, abnormal pulmonary physical signs were present and were thought to be helpful in enabling us to recognize areas of rickettsial pneumonia which were not sufficiently extensive to interfere appreciably with respiratory physiology.

(d) Roentgenography. Roentgen-ray study of patients with scrub typhus rarely brought to light rickettsial lesions which had not been clinically diagnosed.



already, and it usually failed to indicate the extent and severity of the pulmonary process. The patients in whom X ray study might have been done to satisfy clinical curiosity were usually too sick to be moved to the X ray Department, and the bedside X ray apparatus at our disposal did not enable the roentgenologist to obtain films which were clear enough in many cases to be dependable for evaluating the minimal shadows which were present.

(5) *Summary* "Scrub typhus pneumonia" was primarily an interstitial inflammation. It was probably present in some degree in almost all of our cases of scrub typhus. Minor degrees might not be recognizable clinically, or might be suspected on the basis of hearing a few crackling rales, or slight reduction of the breath sounds. When the lesion became extensive enough to become an important factor in prognosis, it reduced the functional capacity of the lungs. This first resulted in intermittent dyspnoea and tachypnoea, then persistent tachypnoea of increasing degree, then cyanosis, relieved initially by oxygen.

The signs of disturbed physiology described above were more useful in diagnosis than physical signs or roentgenographic findings. They were valuable in prognosis because they were among the commonest and earliest evidences of danger to appear.

#### b *Cardiac phenomena*

(1) *Pathological findings* The heart showed characteristic acute inflammatory changes in all fatal cases. Grossly, there was little or no evidence of hypertrophy. Slight to moderate dilatation, predominantly right-sided, was present almost uniformly. In 75 per cent of the necropsies, the myocardium was dull, flabby, and mottled. Microscopically, the muscle fibers often showed a mild to moderate degree of swelling and interfibrillar edema, but the most striking change was the universally present, and often heavy, interstitial infiltration by inflammatory cells—lymphocytes, plasma cells and histiocytes. There were no endocardial lesions or thrombi.

(2) *Clinical phenomena* Soft first heart sounds, systolic murmurs and ectopic beats were common. Transient gallop rhythm was heard frequently. Sometimes it began as early as the fifth day, but usually not until the second week. Persistent gallop lasting three days or more was less frequent. When it did occur, it was almost always associated with increase in heart size. Definite enlargement was diagnosed when the apex impulse was well to the left of the mid-clavicular line, or when the X-ray showed unequivocal enlargement of the cardiac silhouette. Cardiac enlargement began in the second or third week, as a rule, and usually was of a moderate degree. In a few cases, however, the apex reached the anterior axillary line. Cardiac enlargement and persistent gallop rhythm did not appear in mild cases. They were uncommon in moderate cases. Their highest incidence was equally divided among the severe, grave and mortal cases.

(3) *Electrocardiographic findings* Tracings were taken on 35 patients (Group A in figure 23) selected because of severity of disease or a suspected cardiac complication. Subsequently, 26 consecutive patients (Group B) were electrocardiographed on or about the 16th day of fever. This group was also "selected" in

that a number of mild and moderate cases were afebrile by the 16th day and were thus excluded from the group

The number of cases is small and the percentages are not necessarily significant. There was no very striking difference of incidence of abnormalities in the two groups. Thus the incidence of "no abnormality" may be roughly estimated as 16 per cent and the incidence of definite abnormality, about 36 per cent, at least in the sicker cases.

Of the definite abnormalities, PR interval prolongation (fig 24a), which is found in an electrocardiographic study of almost any febrile disease, may not be significant of "myocarditis." The two examples of bundle branch conduction defect may or may not have resulted from typhus myocarditis, since the change persisted throughout the period of observation of the patients. (It is well-known that this type of abnormality may be discovered accidentally in studying a series of "normals.") Sharp T-wave inversion or notching (see fig 25) occurring most conspicuously in lead CR-3, with or without R-ST elevations, was considered the

	GROUP A (35)	B (26)	TOTAL	PER CENT
No abnormality	4	6	10	16
Abnormalities of questionable significance	18	11	29	48
PR interval of 0.20 sec				
Notched, slurred or small QRS (fig 24, e-j)				
Low T-wave amplitude (fig 24, c, d)				
Definite abnormality	13	9	22	36
1 PR interval 0.22 sec or greater (fig 24, a, b)	9	6	15	(25)
2 Sharp T-wave inversion with or without RS-T elevation (fig 25, k-p)	3	4	7	(11)
3 Bundle branch block	1	1	2	(3)
4 Auricular fibrillation (fig 25, q, r)	1	0	1	

FIG 23 ELECTROCARDIOGRAPHIC STATISTICS

most reliable electrocardiographic sign of rickettsial myocarditis. It occurred in 11 per cent of the 61 acutely ill patients who had electrocardiograms.

(4) *Effects of rickettsial myocarditis on cardiac function.* In attempting to determine the effects of rickettsial myocarditis on cardiac function, we were faced with facts which at first glance seemed contradictory—(a) All fatal cases of scrub typhus had extensive myocardial changes at autopsy. Consequently, cardiac failure might have been expected to play an important part in the clinical picture and in mortality. (b) Clinical evidences of cardiac insufficiency during the course of the disease were not very obvious or striking. Cardiac enlargement occurred in 12 per cent of cases, but the mortality of patients with enlarged hearts was no higher than that of an equally sick group of patients without cardiac enlargement. Definite T-wave inversion in the electrocardiogram occurred in 11 per cent of cases who had tracings, yet there was no obvious correlation between electrocardiographic abnormality and mortality. No patient with T-wave inversion died, and none of the three mortal cases who had

tracings before death showed electrocardiographic abnormality. There was no constant correlation between electrocardiographic abnormalities and cardiac enlargement. When edema and hepatic enlargement occurred, more obvious non-cardiac causes for these phenomena were usually apparent (see "edema" and

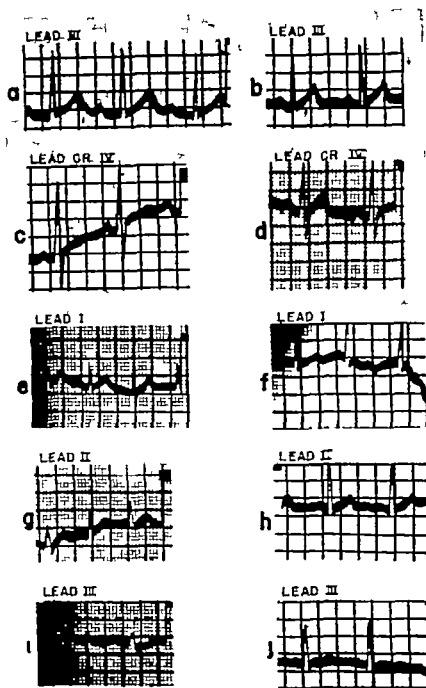


FIG 24

- a Case 176 PR interval prolongation (0.32 sec) after a moderately severe illness on the 25th day after onset. Lead III
- b Case 176 PR interval normal (0.16 sec) on the 79th day. Lead III
- c Case 301 Almost flat T waves in lead CR-4 of a severely ill case on the 16th day of fever. The other leads showed a similar abnormality
- d Case 301 Normal T wave on the 56th day after onset. Lead CR-4
- e g i Case 18 Limb leads of a gravely ill patient on the 15th day of fever. Gallop rhythm and cardiac enlargement were present. The amplitude of the complexes is small. The chest leads were normal
- f h j Case 18 Limb leads on the 44th day after onset showing marked increase of QRS amplitude

'hepatic phenomena" below). The findings in the lungs at necropsy were sufficient alone to account for tachypnoea and cyanosis, and the dramatic relief of the latter by oxygen suggested that circulatory stasis was not its primary cause. Finally, definite signs of congestive heart failure in the peripheral veins and liver

did not appear, even in the patient who developed auricular fibrillation and cardiac enlargement. Patients of all grades of severity tolerated intravenous infusions and blood transfusions given slowly, those with cardiac enlargement as well as those with no clearly demonstrable clinical signs of cardiac abnormality

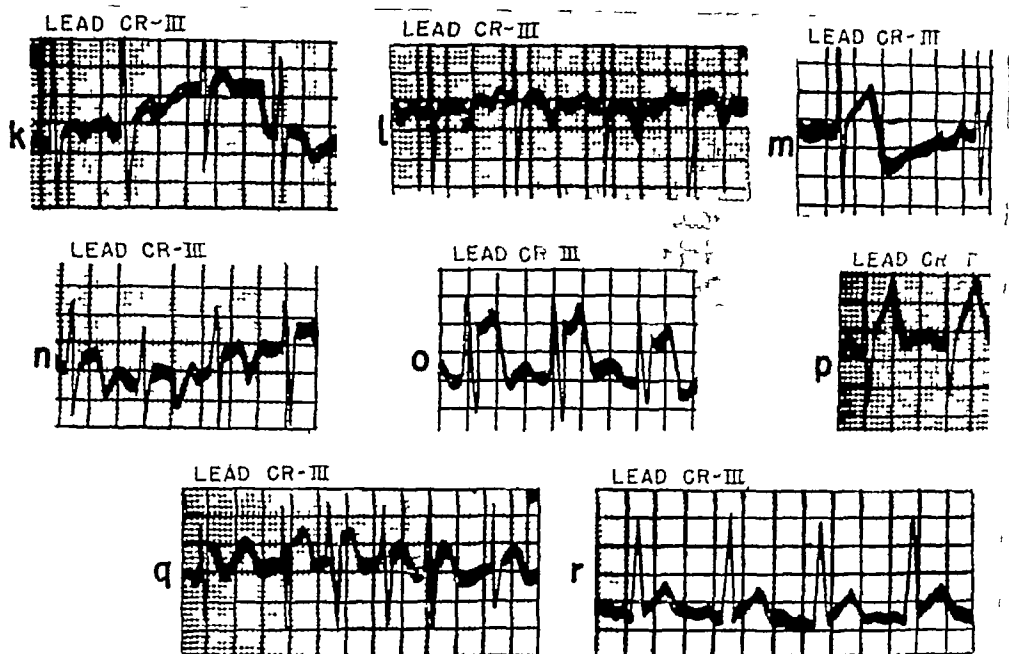


FIG 25

k Case 95 Lead CR-3 on the 12th day of a grave illness. Cardiac enlargement and gallop rhythm were present. There is beginning T-wave inversion. The limb leads showed low T-wave amplitude.

l Case 95 T-wave inversion on the 43rd day in lead CR-3. Cardiac enlargement had decreased, gallop rhythm was still present. All leads showed inverted T-waves.

m Case 95 Normal lead CR-3 on the 110th day after onset. All cardiac abnormalities had disappeared.

n Case 165 T-wave inversion and beginning RS-T interval elevation in lead CR-3 in a gravely ill patient on the 8th day of fever. The heart was enlarged and gallop rhythm was present. The abnormality was less marked in CR-4. Limb leads were normal.

o Case 165 Lead CR-3 on the 45th day after 20 afebrile days. The heart was normal in size but the patient had had a brief attack of dull substernal pain. There is marked RS-T interval elevation (8 mm), which was also present in CR-4 (6 mm) and CR-5 (4 mm). The limb leads showed decreased T-wave amplitude.

p Case 165 Lead CR-3 on the 65th day, showing a normal tracing.

q Case 180 Auricular fibrillation on the 12th febrile day in a severely ill patient. Lead CR-3 shows RS-T interval elevation of 5 mm in some complexes. The remaining leads were normal except for the arrhythmia. The heart was enlarged and gallop rhythm was present. There were no signs of congestive heart failure. The fibrillation lasted 24 hours and ceased spontaneously. Cardiac enlargement lasted five days.

r Case 180 Lead CR-3 on the 31st day after onset, showing return to normal.

There seemed little doubt, however, that a gross and histologic picture such as that seen at autopsy could have failed to be associated with important disturbances of cardiac physiology. Many patients with severe scrub typhus must have had impaired cardiac function, although they did not show the classical signs of peripheral venous and hepatic congestion. Some of the phenomena which we have attributed to typhus pneumonia (tachypnoea, dyspnea and cyanosis) may

well have been contributed to by cardiac insufficiency. However, terminal pulmonary edema was probably due to some cardiac failure.

Since these clinical signs of cardiac abnormality which were noted enlargement, T-wave changes and persistent gallop rhythm were not found to be harbingers of grave illness or death, it seemed probable that we could not disguise dangerous cardiac damage or predict impending cardiac disaster, as we could often do in the case of pulmonary damage.

(5) *Summary:* Prolonged hypoxemias of some degree probably occurred in most of our patients with scrub typhus. In many cases the cardiac changes were severe and extensive. In some cases a cardiac lesion was recognized on the basis of cardiac enlargement or T-wave inversion in the electrocardiogram. However these observations did not carry a higher mortality than that observed in severe scrub typhus in general.

Thus it was difficult to escape the conclusion that we had not been able to recognize dangerous cerebral hypoxemias before the advent of terminal pulmonary edema. The only safe course to pursue was to treat all severe scrub typhus on the assumption that a serious impairment of cardiac function existed.

### c. Nervous system picture

(1) *Pathologic findings:* All scrub typhus patients showed lesions in the nervous system. Grossly, the changes were not very striking. There was some meningeal congestion, often the pre-arachnoid had a slightly milky appearance, especially over the cerebral hemispheres, occasionally there was moderate edema of the brain with some distending of the ventricles. In two cases there were small hemorrhages, one subdural and one subarachnoid. The cut surface of the brain revealed marked small vessel congestion, and occasionally a few minute hemorrhagic foci. Gross hemorrhage into the brain substance was never encountered.

The microscopic picture was one of meningoencephalitis. A moderate to heavy round cell and histocyte-free cell infiltration of the arachnoid was uniform. Rarely a small zone of hemorrhage into the arachnoid was encountered, or a small meningeal vessel presented a recent fibrinous thrombus. Within the brain substance the inflammatory reaction varied from slight to moderate with round cells predominating and showing a marked tendency to collection about and in the walls of capillary and larger vessels. Heavy cuffing of the type seen in Rocky Mountain spotted fever was never encountered. The reaction was widely distributed through cortex, basal ganglia, cerebellum, pons and medulla. Cells were not regularly, it appeared somewhat more intense in sections from the brain stem. A few scattered, tiny, punctate hemorrhages could usually be seen in the subcortical and pontine tissue. Capillary congestion was uniform, whereas the endothelium usually showed little reaction, though sometimes vessels contained endothelial swelling partially obstructing the lumen. A slight to moderate increase in small round glia cells in cortical areas was the rule. Occasionally these cells appeared in satellite grouping about nerve cells in the cortex. When routine histologic stains it was usually not possible to demonstrate any significant degree of nerve cell abnormality, though some rather suggestive changes

was not infrequently apparent. Minute areas of granular degeneration, with focal infiltration by round cells, monocytes and an occasional polymorphonuclear leucocyte were present in a few cases. As a rule, these areas were found in the cortical nerve cell layer or in the pons.

(2) *Clinical phenomena* The pathologic findings were reflected in the clinical pictures of the 200 cases in a number of different ways.

(a) *Meningeal signs* Twenty-seven patients (13.5 per cent) had pain and tenderness in the neck muscles and some resistance to flexion. Only a very few had marked cervical rigidity. Lumbar punctures were performed on all twenty-seven cases. The pressure varied from 90 to 380 mm. of water, averaging 230. The cell counts recorded in 25 of these patients were as follows: 15 had fewer than 10 white cells per cubic millimeter, four had from 10–15 cells, the remaining six had counts ranging from 90 to 510 cells. Mononuclear cells predominated in all but three cases. Two of these three with polynuclear pleocytosis had the highest cell counts in the entire group. They were suspected of having an intercurrent pyogenic meningitis and were treated as such despite negative cultures. Both survived. The Pandy reaction was mildly positive on the fluid of nine of the seventeen patients for whom it was done. Quantitative protein figures (four cases) ranged from 68 to 156 mgm. per cent.

These meningeal signs appeared in moderate as well as severe cases and did not necessarily signify more serious prognosis than severe illness in general, although the mortality of the group which had them was 30 per cent.

(b) The following minor signs of generalized cerebral involvement occurred:

Hyperesthesia appeared in five per cent. It occurred in the first week as a rule and had no prognostic significance.

Marked apprehension appeared in the first week in ten per cent and tended to persist through the febrile stage.

Apathy and drowsiness were common in the second week.

Transient mental confusion occurred in 22 per cent, usually at night, or at the peaks of fever.

A marked coarse intention tremor appeared during the second or third week in 13 per cent and persisted for two to eight weeks, often, in fact, well into convalescence.

In a considerable proportion of severe cases, subsultus tendinum appeared. This consisted of uncoordinated, intermittent jerkings of small muscle groups, particularly those of the upper extremities and the face. In a small proportion of very ill patients, these myoclonic jerkings became so severe that the patient looked as if he were having a continuous chill.

(c) Major signs of generalized involvement of the brain were as follows:

Delirium occurred in 26 patients (13 per cent). It usually began late in the second week or early in the third, after a period of mild confusion. In most cases there were poorly organized terror states, usually constructed around recent battle experiences. Such patients were very prone to attempt escape from the ward, or to take refuge under their beds. They required vigilant supervision. As a rule, delirium disappeared with defervescence. In seven patients, who had

developed more highly organized delusional systems, these persisted through the first two or three weeks of convalescence. In two patients, defective judgment persisted until well after return to the United States, following two months of convalescence. Delirium did not appear in mild cases. It was seen occasionally in the moderately ill. It was commonest in the dangerously ill.

Twenty six patients developed a peculiar, persistent restlessness. Such individuals would not lie quietly, but constantly thrashed about, sat up, or tried to get out of bed. They would not tolerate an oxygen mask, or an intravenous infusion. They required constant nursing supervision and sedation. They were all gravely ill and wore themselves out at a time when their physical reserves were precariously low.

Twelve of the 200 patients had convulsions, varying from the severe clonic jerking type resembling a chill, to major epileptiform seizures. They occurred as a rule in the third week, although one patient had a convulsion on the sixth day. Nine of the twelve had shown previous evidence of dangerous illness with severe involvement of the brain, lungs, or heart. In three instances, however, the convulsion came suddenly and unexpectedly in patients who were not considered dangerously ill. Nine of these patients died within six hours after their convulsion. One survived for three days, only to die after a second convulsion. Two recovered.

Coma occurred in fourteen patients. In two, the onset was gradual. In the other twelve it followed a convulsion. All but one of these individuals died.

(d) Miscellaneous signs. In addition, certain miscellaneous signs seemed to be related to the central nervous system inflammation. These were persistent hic-cough, which occurred in eight patients, all of whom were seriously ill, urinary and fecal incontinence, present in 14 gravely or mortally ill patients, and Cheyne-Stokes respiration, which was of grave import, 12 of the 14 patients who had it failing to survive.

(e) Focal central nervous system damage was rarely evidenced but was suspected in a few cases. Five patients had difficulty with speech or deglutition. Thus dysarthria and dysphagia may have been partially or wholly due to co-existent stomatitis and not to a bulbar palsy. No definite spinal cord lesion was seen in this hospital, but in another installation one of the authors observed a patient with paraplegia and urinary retention which disappeared in convalescence and appeared to be due to spinal cord involvement.

(f) Peripheral nerve signs. The majority of patients with scrub typhus complained of deafness during the second or third week. Usually tinnitus accompanied it. In a few instances, this was due to quinine administration or otitis media. In most, however, it was thought to be a true neural deafness. It usually disappeared with defervescence but occasionally persisted for weeks or months. Partial or complete unilateral peripheral seventh nerve paralysis occurred in three cases during their acute illness. All cleared promptly with defervescence.

A few patients developed paresthesia, numbness and weakness in the ulnar nerve distribution which persisted for several weeks but finally cleared. One

patient, who was originally suspected of having a central monoplegia of the right arm, subsequently developed a definite brachial plexitis with atrophy of muscles and anesthesia over the back of the upper arm, the shoulder and the scapula.

(g) "Tender toes" The minor degrees of tender feet were described in the section on the "textbook picture" of moderate scrub typhus. In these patients the pain was only elicited by vigorously squeezing the toes. The sign disappeared with defervescence.

Five patients had severe spontaneous pain in the feet after defervescence, as exemplified in the case described under the clinical picture of "Dangerous Scrub Typhus". They complained bitterly of this pain when their feet were exposed to changes in temperature, or to the slight pressure of bed clothes or to washing. The phenomenon persisted well into convalescence, and prevented walking and normal rehabilitation for a long time. It did not occur except in those who had been very ill. There was no clinically demonstrable lesion of the peripheral nerves or blood vessels in these cases.

(3) *Summary* Meningoencephalitis was found in all scrub typhus cases at necropsy. There was reason to think that the central nervous system was involved at least slightly in almost all patients. The meningeal involvement did not always produce clinical signs and even when these occurred they indicated a severe, but not necessarily a grave, illness. Confusion, tremor and myoclonia were common. Delirium occurred frequently in the dangerous group. Malignant restlessness or convulsions were among the most ominous signs of the disease, and coma was usually followed by exitus.

#### d *The kidney, fluid balance and chemical regulation*

(1) *Pathologic findings* The renal picture presented great variation. Some kidneys were practically normal. Others showed moderately severe acute damage.

In the average case, with antemortem evidences of moderate dysfunction, the picture was that of a mild acute nephritis with some special characteristics to be noted.

The kidney was usually dusky and swollen. There was moderate to severe gross congestion, some blurring of landmarks, and, as a rule, submucosal petechiae in the pelvis. Microscopically in these cases the glomerular tuft was swollen, with the capillary membrane thickened and the lumen often nearly bloodless. Some prominence of capillary endothelium was the rule. Extravasation of red blood cells into the glomerular space was not seen, and leucocytic infiltration was almost entirely absent in the tuft itself. No damage to glomerular arterioles was discovered. No thrombi were seen. Changes in the tubules were usually considerable, with swelling and granularity of tubular epithelium, and occasionally some desquamation. Granular casts were usually numerous in tubular lumina, and much albuminous precipitate was the rule. A few hemoglobin casts were often encountered.

Most characteristic of the disease, however, was interstitial infiltration by inflammatory cells of varying but often quite intense degree. The cells were



predominantly lymphocytes, usually rather immature in appearance. Plasma cells were often numerous also. These tended to follow the course of the striate vessels of the cortex and medulla, giving a streaked appearance to the tissue. A moderate degree of interstitial edema was often apparent. Congestion of interstitial capillaries was the rule. Hemorrhage was found only as petechiae in the submucosa of the renal pelvis and was never extensive in this area.

Increased tissue fluid was observed at necropsy in 30 per cent of cases. Two patients had a small ascites, 300 and 400 cc of sterile, cloudy, yellow fluid respectively. Three other cases had gelatinous edema in the retroperitoneal tissues. Chemical analysis of the edema fluid was not carried out.

(2) *Clinical phenomena (based on an analysis of 150 consecutive cases)* Attention was first directed to the renal manifestations of scrub typhus by findings encountered in an American officer patient admitted in November 1943. During a very grave illness, he had massive albuminuria, many coarse granular casts in the urinary sediment, fixed urine specific gravity, and, although the daily urinary output was 2500 to 3000 cc, his blood urea nitrogen remained over 50 mgm per 100 cc for more than ten days with the maximum figure 140 mgm per 100 cc. A transient hypertension (140/100) during the early period of his convalescence was the only residuum which could be interpreted as of renal origin. This case was of more than average severity but illustrates many of the laboratory and clinical changes to be described below.

(a) *Albuminuria* Albuminuria in some degree occurred in most of the cases. Moderate ("two-plus") or marked albuminuria occurred in 24 per cent of the cases, usually during the second and third weeks, but sometimes as early as the first few days. It was more frequent in those in whom the disease was severe than in the milder cases.

(b) *The sediment* Urinary casts, other than a few hyaline casts, were observed only in patients with albuminuria and especially in those with massive albuminuria. They were characteristically quite uniform in size and shape, extremely coarse, granular, often dark brownish yellow in color, and frequently present in enormous numbers. The paucity of other sediment abnormalities was striking.

Red blood cells were present in the urines of only nine per cent of the cases, and in these patients only in very small numbers.

(c) *Reduction in urine concentration* In 21 per cent of the cases, the specific gravity remained between 1.009 and 1.011 in repeated observations. This isosthenuria, when present, occurred during the latter part of the second week and in the third week of illness. In some instances it was coincident with a rising blood urea nitrogen and definite oliguria, and was commonest in the grave and mortal cases, about 40 per cent of whom showed this finding. This isosthenuria was clearly distinguishable from the low specific gravity (usually well below 1.010) associated with convalescent clearing of extracellular fluid.

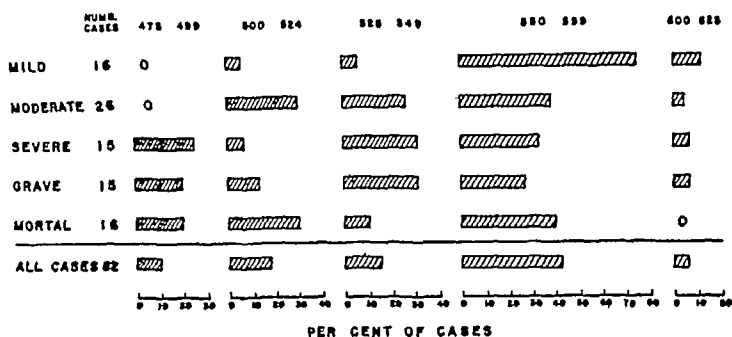
(d) *Reduction in urinary volume* The urine volume of most patients was large, as an intake of 2500 to 3500 cc of fluid per day was maintained. A 24-hour urine volume reduced to 500 cc or less, persisting for one to three days, occurred in 13 per cent of the cases, one quarter of whom had complete anuria for one or



acute phase of the disease, in general falling in the low normal range (550 to 580 mgm per cent) in the milder cases, lower in the more severe cases. Very low levels (below 500 mgm. per cent) were observed in eight patients, all of whom were gravely ill (fig 27). Edema and ascites were more frequently observed in the hypochloremic patients, than in the group as a whole. Not much effect on the chloride levels was produced by the administration of parenteral saline solution. The return to normal regularly occurred during the early convalescent period regardless of the therapy employed. In the 13 patients, all gravely ill, for whom carbon dioxide combining power of the plasma was estimated, all levels were below 55 volumes per cent, the majority lying between 30 and 40, with two below this range. Since the chloride levels frequently were also low, it can be reasoned that a significant lowering of total base occurred.

### SERUM CHLORIDE

Mgms. NaCl per 100 ccm.



PER CENT OF CASES  
FIG 27 SERUM CHLORIDE LEVELS

The lowest figures obtained in determinations on 82 cases are given, expressed as per cent of the total of each severity group

(j) Hypoproteinemia. Serum protein levels were above 6.0 grams per cent in two-thirds of the cases. Ten per cent were definitely low (below 5.0 gms per cent), the remainder being intermediate. There was no regular correlation of hypoproteinemia with any other clinical manifestation, including severity of illness and edema. Albumin globulin ratios were not determined in American patients. A few determinations on Chinese scrub typhus cases revealed a lowered serum albumen with increased globulin and reversal of the ratio, although the total serum protein values were normal.

(k) A slight but definite hypertension in the early convalescent period was observed in two patients, in both of whom the acute phase of the disease had been grave. The highest level was 160/110 and in this patient there was retinal arteriolar spasm. The other patient was Case #95 (see case report). In neither instance did the hypertension last longer than one month.

(3) *Discussion* The occurrence of heavy albuminuria and cylindruria, isosthenuria, marked oliguria or azotemia exceeding 50 mgm of blood urea nitrogen per 100 cc all justified assigning any patient to the "dangerous" group. Although a third of the autopsied cases had clinical and pathologic evidence of acute nephritis and the statistical mortality of patients with renal dysfunction was high, we did not feel that the kidney lesion was as important as other factors in determining the outcome. In the absence of major pulmonary and cerebral dysfunction, patients manifesting signs of nephritis invariably survived, including a case, whose blood urea nitrogen reached 140 mgm per 100 cc.

Pitting edema, ascites and hypochloremia below 500 mgm of NaCl per 100 cc were confined to severe illnesses. Slight fluid retention, evidenced mainly by a diuresis near the end of the febrile period was not indicative of severity and, with slight hypochloremia or azotemia, could occur in moderate or even mild illnesses. Diuresis was one of the most reassuring of prognostic signs, no patient in our experience died after this was well established.

Fluid retention in scrub typhus was not clearly explained by our data. It may depend upon the combination of several factors. Although we did not study enough albumen-globulin ratios to be sure of the frequency of albumen reduction, we suspected that the change in plasma osmotic pressure was probably important. In addition, the renal lesion combined with reduction of renal circulation probably played a part in patients who had oliguria.

The hypochloremia was comparable in degree to that reported in lobar pneumonia. Its mechanism could well have been similar. That is, a shift of electrolyte to the tissues, rather than actual loss of base from the body. This might also have been a factor in fluid retention.

(4) *Summary* Evidences of acute nephritis were found in about one-third of scrub typhus necropsies. The more frequent laboratory findings included albuminuria, coarse granular casts, isosthenuria, moderate azotemia and in rare cases anuria and uremia. Hypertension occurred during convalescence in an occasional case.

Fluid retention was manifested as oliguria with subsequent diuresis, and less often, as generalized edema with or without ascites. The serum chlorides were frequently below normal. Total serum proteins were usually within normal limits but sometimes subnormal levels were found. Albumen-globulin ratios were not done routinely, but a few determinations in Chinese patients showed a reversal of the ratio.

#### e *Hepatic phenomena*

(1) *Pathologic findings* At autopsy the liver was enlarged (1700-2400 grams) and presented a dry cut surface with indistinct lobular markings. Microscopically, a moderate granular degeneration of parenchymal cells was seen, with occasionally slight fatty metamorphosis. Occasionally some disorganization of cell columns was noted but there were no areas of necrosis. Widening of the portal areas by cellular infiltration, mostly lymphocytic and monocytic but occasionally with a moderate proportion of polymorphonuclear leucocytes, was usual, but mild in degree. Often inflammatory cell accumulation along the cell columns,

but within the sinusoids, was a noticeable feature. Evidences of passive congestion were not seen.

In the three cases coming to postmortem with a history of jaundice, no essential differences from the above picture could be found, nor was the intensity of histologic change recognizably greater.

(2) *Clinical findings* The frequency of moderate liver enlargement and tenderness has been mentioned. Enlargements occurred in all grades of disease severity. Tenderness was more common in severe cases but did not increase in frequency in the gravely and mortally ill. No liver function test was done except for a small number of prothrombin times, which tended to be slightly low. These are discussed in the section on Hemorrhagic Phenomena. There were no other gross signs of liver failure except for icterus in six of 200 cases, averaging 5.7 mgm per 100 cc of bilirubin.

Icteric patients were of two types. Three of the six had jaundice of five, eight, and 23 days' duration, with the onset between the seventh and the tenth day of disease. The patient with the most marked icterus was only moderately ill, although he developed ascites. Because catarrhal jaundice was occurring in the organizations from which these patients came, the possibility of a complicating disease could not be excluded. Jaundice did not occur in 250 subsequent cases of scrub typhus.

The remaining three icteric patients were mortally ill. They developed jaundice in the third week of disease, from two to five days before death. All had "typhus pneumonia" and grave meningoencephalitis. Two were uremic. They were the only cases in the series with appreciable microhematuria, 20-30 red blood cells per high power field being found in the urinary sediment.

(3) *Summary* Varying degrees of cloudy swelling and parenchymal degeneration occurred in the livers of scrub typhus cases. These changes were manifested clinically by enlargement and tenderness of the liver in a minority of patients. Liver failure was very rare and occurred only with other evidences of overwhelming infection.

#### f Hemorrhagic phenomena

(1) *General* The hemorrhagic phenomena seen in 200 cases are listed in figure 28. Slight subconjunctival, pulmonary and nasal bleeding was occasionally seen as an isolated phenomenon in cases whose illness was not severe. Otherwise, there was a direct correlation of hemorrhagic manifestations with severity as the table shows. In addition to those listed, all fatal cases showed multiple petechiae beneath serous surfaces, particularly the pleura, epicardium and renal pelvis. Microscopic cerebral hemorrhages were also usually seen.

(2) *Gastrointestinal* The only massive hemorrhages in our experience were gastrointestinal. They were responsible for two deaths in 500 cases, and two other patients were placed in grave danger. Smaller amounts of bleeding also occurred. These hemorrhages were sudden and unpredictable. They might occur at any time after the first week and in patients whose degree of illness was otherwise only moderate. No ulceration or bleeding points were found at autopsy in the two fatal cases, although the Peyer's patches were hypertrophic.

Approximately three liters of blood were found in the gut of the two fatal cases. In one survivor, the hemoglobin fell from 13.0 to 5.2 grams.

(3) *Other hemorrhagic phenomena* Hemoptysis usually was insignificant. However, two mortal cases expectorated almost pure blood for two days before exitus. Two localized subdural hemorrhages occurred. Massive intracranial bleeding was not seen though it has been reported from other installations in this area.

(4) *Gangrene* Gangrene was seen only once in a very ill patient who had a gangrenous ulceration of the lip. The rarity appeared to be explained by the fact that fibrinous thrombi were almost never found at autopsy.

(5) *Abnormality of the clotting mechanism* The hemorrhagic manifestations of scrub typhus appeared for the most part to be related to capillary damage.

	SEVERITY GROUPS					
	Mild	Moderate	Severe	Grave	Mortal	Total
Number of patients	61	68	36	18	17	200
Number showing any hemorrhage	2 (3%)	6 (9%)	10 (28%)	10 (55%)	17 (100%)	56 (28%)
Types of hemorrhage						
Subconjunctival	1	3	3	6	5	18
Epistaxis	1	0	3	4	2	10
Hemoptysis	0	3	2	1	2	8
Oral Bleeding	0	0	0	2	5	7
Ecchymosis	0	0	0	2	3	5
Intestinal						
small	0	0	1	1	1	3
massive	0	1	0	0	1	2
Subarachnoid	0	0	0	0	1	1
Retroperitoneal	0	0	0	0	1	1

FIG. 28. INCIDENCE OF HEMORRHAGIC PHENOMENA IN 200 CASES

However, Captain H. H. Hodges discovered certain abnormalities in the clotting mechanism which may have been contributory. One or more coagulation time determinations (10 mm. tube) were made on 28 patients, selected from a total of 150 because of a bleeding tendency (bowel hemorrhage, excessive epistaxis, subconjunctival hemorrhage), a very florid rash, or a severe illness. Prothrombin levels were determined for eight of these cases. The results were as follows:

COAGULATION TIME	CASES	PROTHROMBIN ACTIVITY	CASES
Less than 20 min	12	75-100%	2
20 to 30 min	5	65- 75%	0
30 to 40 min	4	55- 65%	2
40 to 60 min	5	45- 55%	3
Over an hour	2	35- 45%	1

Two of seven patients with prolonged coagulation time also showed incomplete clot retraction in 18 hours and unequivocally low platelet counts. Their bleeding time was prolonged and the tourniquet test was strongly positive.

These abnormalities of clotting mechanism were treated with parenterally administered vitamin C and K, which were given to all patients who showed hemorrhagic manifestations. Clotting time returned to normal in all cases within six days after institution of therapy. Five days after treatment was begun, prothrombin levels were 100 per cent in the only two patients in this group on whom this test was done. This suggests that liver injury could not have been severe.

Thus, a considerable proportion of patients with severe scrub typhus when tested showed abnormality of the clotting mechanism. A somewhat lowered prothrombin level was frequently associated with prolonged clotting. Since prothrombin in the range of 50 per cent of normal is not low enough to prolong the clotting time, other unknown factors must have been operative.

#### *g Excessive fever*

The character of the fever curve and the total duration of pyrexia in scrub typhus cases have been described in a previous section and in figure 13. The latter illustrates the impossibility of correlating severity of disease with duration of fever except in a general way. The height of the fever, however, and the frequency of occurrence of high temperatures was often of prognostic value.

Low fevers, not exceeding one day at  $104^{\circ}$ , were confined to the mild and moderately ill and no patients with this degree of fever died. Several spikes to  $104^{\circ}$  frequently occurred in the moderately ill and were not cause for alarm, but only the severely ill had this much fever for more than a week. A single day at  $105^{\circ}$  did not appear to be very significant.

Very high fever,  $105^{\circ}$  or more for three or more days, was found to have an ominous import. Fifty per cent of patients who manifested this died. Even a single spike to  $106^{\circ}$  justified alarm.

Thus, extreme fever had much the same prognostic significance as the various signs of major organ dysfunction which have been discussed in this section. Such patients were always severely ill, although gravely ill patients always had signs of major organ dysfunction as well. Seventy-six per cent of 17 deaths had excessive pyrexia. Very high fever was an important manifestation of dangerous illness even though many dangerously ill patients failed to have this sign.

#### *h Summary of diagnostic signs and their prognostic value*

*General* In the average case of scrub typhus, during the first week there were no signs by which the probable outcome could be determined. Occasionally a high fever at this time indicated a severe course. During the second and third weeks, however, certain phenomena appeared which justified placing the patient in the "severe" or the "grave" groups with respective mortalities of approximately 25 per cent and 50 per cent. However, until the disease was definitely on the decline one could not be sure that these features would not appear. Conse-

quently, the diagnosis of mild or moderate scrub typhus, which carried practically no mortality was not justified until defervescence was definitely established. These categories were useful primarily in the management of convalescence, not in prognosis.

A case of scrub typhus was assigned to the "severe" group on the basis of any one of the following

- (1) An alarming increase of the general evidences of illness in the second week
- (2) More than the usual amount of fever over a week of peaks to  $104^{\circ}$ , or  $105^{\circ}$  for more than two days
- (3) Frank clinical signs of dysfunction of an important organ
  - (a) Signs of "typhus pneumonitis" Respirations 36/min 2 days, cyanosis of the skin
  - (b) Signs of meningoencephalitis Severe delirium, meningismus
  - (c) Signs of nephritis. Azotemia over 50 mgm per cent, isosthenuria, heavy albuminuria and cylindruria
  - (d) Marked enlargement of the heart or sharp T-wave inversion in the electrocardiogram
  - (e) Pitting edema with or without ascites
  - (f) Multiple hemorrhagic phenomena

The appearance of any of these phenomena indicated that statistically the patient's chances of survival had been reduced from 19 in 20 to about three in four.

A severe case of scrub typhus was considered in the "grave" group on the basis of one of the following findings

- (1) A steady increase of illness during the third week
- (2) Very high fever  $105^{\circ}$  for five days or  $106^{\circ}$  for two days
- (3) Signs of severe dysfunction of more than one vital organ, or evidence of severe inflammation of the central nervous system and the lungs. Of these, the most common were the following
  - (a) Extensive pneumonitis Persistent cyanosis out of oxygen, respiratory rate 50/min for two days, or over 36/minute for a week
  - (b) Encephalitis Malignant restlessness, Cheyne-Stokes respiration, a convulsion, coma
  - (c) Severe nephritis Anuria
  - (d) Tachycardia exceeding 130 per minute

The appearance of these phenomena indicated that, statistically, the patients' chances for survival were 25 to 50 per cent. We have never seen a patient recover whose cyanosis was unrelieved by oxygen or who had persistent hyperpnoea, pulmonary edema or coma lasting 24 hours. Figure 29 is an analysis of the statistical prognosis of a group of ominous phenomena.

#### 1 *Extrinsic factors influencing severity*

Although in the first week, no individual case can be classified as mild, moderate or "dangerous", two factors clearly influenced the percentage of patients who fell ultimately into the various groups. The first was the general condition of the



patient before he developed the disease. Malnutrition, exhaustion, and the occurrence of other diseases, principally dysentery and malaria, raised the statistical chance of developing severe scrub typhus. Secondly, the availability of good medical care in the first week seemed to be very important. Patients who had to continue marching and fighting for tactical reasons during the early days of their infection were much more likely to become severely ill. This was well illustrated by the high morbidity and mortality in the outbreaks among troops who were actually engaged in active jungle combat (groups 3 and 5, figs 1 and 2).

It can be seen from the tables on incidence of severity in our five groups of patients (fig 2) that the great variable is the number of severe cases and the degree of this severity, i.e. the number who became gravely and mortally ill. Since the relative proportion of mild cases was fairly constant in all outbreaks, the number of moderate cases varied inversely with the number of severe infections. Thus it would appear that it was the moderately ill patient who was most adversely affected by deficiencies of early care and that severe cases were re-

	TOTAL CASES	DEAD	MORTALITY
			%
Convulsions	12	11	92
Cheyne-Stokes respirations	14	12	87
Respiration reaching 50/min for 2 days	5	4	80
Anuria (12 hrs or more)	4	3	75
Hiccough	8	5	63
Fever reaching 105° on 5 days	24	13	55
Malignant restlessness	20	13	50
Tachypnoea 30/min for 7 days	22	10	45
Tachycardia over 130/min	27	12	44
Cyanosis	36	14	39

FIG 20 OMINOUS PHENOMENA

cruted mainly from this group. It must be admitted, however, that the factors of individual resistance to infection and variations in rickettsial virulence in different foci cannot be evaluated in the present state of our knowledge.

Awareness of the patient's pre typhus state of health and the quality of his early care was important in prognosis, but where these factors were not operative there was no guarantee that grave or mortal illness would not occur. One of our fatal cases among the service troops was in excellent health before he developed scrub typhus and was admitted for a minor complaint before the onset of fever. In spite of all our efforts, he died in 14 days (fig 21).

## 6 CONVALESCENCE

### a. Complications of the first two afebrile weeks

During the first two afebrile (or subfebrile) weeks, certain complications might occur for the first time.

The most serious was a sudden convulsion followed by exitus. This did not happen in our hospital experience, but at least two instances occurred in other hospitals in this area. There seemed to be no way of predicting or preventing this rare disaster.

Intestinal hemorrhage might occur as late as the end of the second week of convalescence. It nearly caused the death of one of our patients whose acute illness had been only moderate.

Thrombophlebitis occurred occasionally. It might be manifested only as a low unexplained fever for many days, or by pain in the calf and toes of the affected leg with a positive Homan's sign, clearcut findings of venous obstruction developing later.

Pulmonary embolism complicated at least three of our cases of thrombophlebitis. The occurrence of hemoptysis in convalescence strongly suggested such a diagnosis. None of the emboli were lethal.

Post-typhus pleurisy. This complication occasionally appeared during defervescence but was usually delayed for days after the fever subsided. Ten per cent of the statistical series of 200 developed pleurisy. Pain in the chest, the shoulder or the upper quadrants of the abdomen was the earliest diagnostic sign. Sizeable effusions did not occur, and small amounts of fluid, when present were sterile. Fever was usually in the vicinity of 100-101°. In most cases, the fever disappeared in four days, and the clinical evidences of pleurisy subsided in seven days.

Subcutaneous abscesses or suppurative lymphadenitis, usually staphylococcal, occurred occasionally in greatly debilitated patients.

Subdeltoid bursitis was occasionally seen.

The syndrome of "tender toes" has already been described, it complicated the convalescence of a few severe cases.

One and three-tenths per cent of cases developed uveitis early in convalescence. This subsided uneventfully in all but one patient who developed a secondary glaucoma.

#### b *Subsequent course*

(1) *General*. After the first two weeks, new symptoms were rarely associated with organic disease unless accompanied by objective signs. Patients complained of a variety of things: precordial pain, sometimes referred to the shoulder or arm, palpitation, subjective exertional or nocturnal dyspnoea, vertigo and tinnitus aurium. Many were nervous, hypochondriacal and querulous.

(2) *The heart after defervescence*. Evidences of cardiac enlargement disappeared within two weeks after convalescence began except for Case #95, in whom it persisted for over three weeks. P-R interval prolongation likewise returned to normal within two weeks except in two cases in which it lasted three and eight weeks respectively (fig 24a).

RS-T segment deflections and T-wave inversions in the chest leads tended to persist longer: one case two weeks, one case four weeks, two cases five weeks and one eight weeks after the subsidence of fever (fig 25). Furthermore, in two cases,

the electrocardiographic changes increased during early convalescence and were maximal in the third afebrile week (fig 25, 1, o)

The symptom complex known as the "effort syndrome" often appeared in convalescence. As far as we could tell, it bore no relation to rickettsial myocarditis, and was a product of general weakness and neuropsychiatric factors.

Because certain statements had appeared in the literature concerning heart disease persisting after scrub typhus, we made a careful cardiovascular study of 25 unselected mild, moderate and severe cases, after reconditioning for combat duty had been completed. All findings were normal, including physical examination, blood pressure, electrocardiogram, cardiac size by chest film and fluoroscopy, and exercise tolerance. The most dangerously ill cases did not appear in this group since most of these were dispositioned to the Zone of the Interior.

## 7 THERAPY AND MANAGEMENT

### a. *Acute scrub typhus*

(1) *Mild and moderately severe scrub typhus* There are four essentials in the treatment of all scrub typhus cases: rest, nutrition, fluids, and adequate nursing care.

*Rest* It is common to find scrub typhus cases in the first week who do not feel extremely ill and who are anxious to have latrine privileges. It is also common to see patients whose first week of disease is very mild, who develop high fever and signs of major organ damage in the second week or later. It is impossible to predict which cases these will be. Consequently every effort should be made from the outset to prevent depletion of resources and to prepare the mildest-appearing case to withstand a major ordeal to come. *Absolute rest should be insisted upon from the earliest possible moment, no matter what the apparent degree of severity.*

A Gatch frame or other support is necessary to insure the maximum rest, since patients persist in trying to sit up in bed and usually desist if placed in a semi-Fowler position. Sedation with barbiturates or chloral hydrate should be used when necessary.

*Nutrition* It has often been said that scrub typhus patients will not eat. However, the truth of the matter is that in most instances *the patients will not make an effort to nourish themselves*. They are apathetic and weak rather than capriciously anorexic. If an attendant places a tray of food on the side table, the patient will make little attempt to eat. When we established the procedure of plying the patients with small sandwiches and nutritious fluids every two hours, and of having the nurse actually feed the sicker patients, the vast majority attained an adequate caloric intake. The Red Cross personnel who volunteered for this service during an emergency may well have saved a number of lives.

A semi-soft diet high in protein and carbohydrate is indicated. A rare case may require tube feeding. "Shotgun" vitamin therapy was used in all cases. Vitamin K was given parenterally to all jaundiced patients and to a number of others who showed hemorrhagic tendencies and a somewhat low prothrombin activity.

*Fluids* These patients required a large fluid intake. Fluid loss from the skin was high. Drenching sweats occurred during the remissions of fever, and insensible perspirations must have been great when the fever was high. In monsoon heat, this loss was further exaggerated. We administered a minimum of three liters of fluid a day to all patients and attempted to maintain a urinary volume of between one and two liters per twenty-four hours. This was particularly important in the presence of azotemia, and even in the presence of pitting edema we attempted to keep the urine volume large, although the chloride intake was kept low in such cases.

In almost all patients this fluid intake was attained by oral administration, but when intravenous infusions were necessary we gave them slowly and without incident. (Five per cent glucose in water was generally used.) We never saw an instance where untoward effects could be attributed to an infusion, even in patients with cardiac enlargement or other evidence of myocarditis. Intravenous fluids should not be withheld when clear indications for them exist.

Salt administration in scrub typhus can easily be overdone. Even when serum chlorides were very low, it was impossible to raise them much without causing edema. Consequently we supplemented the dietary intake with small amounts of oral sodium chloride or with physiologic salt solution when parenteral fluid was given for other purposes, but never permitted the total salt intake to exceed ten grams a day, usually only one or two grams when the dietary seemed properly balanced.

*Nursing care* The importance of staffing a typhus ward with nurses experienced in caring for patients with this disease cannot be overemphasized. The administration of food and fluid, the care of the mouth and skin, the fine adjustments of sedation and oxygen therapy, and the ceaseless vigilance required in keeping patients in a state of rest and confidence calls for the utmost in nursing competence. We believe a scrub typhus patient is far better off with experienced nurses and a doctor who has only average knowledge of the disease than would be the case if the reverse were true. Although at first we isolated patients carefully, fearing transmission of the disease in the hospital, no case of hospital infection was ever seen, and isolation was discontinued.

(2) *Dangerous scrub typhus* When evidences of a severe infection appear, three additional therapeutic measures may become essential. These are oxygen, blood transfusions and heroic sedation.

(a) *Oxygen* Oxygen was administered to all cyanotic patients, usually at eight liters per minute, by means of a BLB mask of the closed type. Cyanosis usually disappeared within a short time after oxygen was begun. Later, in the course of the disease, if cyanosis persisted despite oxygen, death always occurred. One might think that oxygen should have been started when tachypnoea appeared, before frank cyanosis became evident. We have not found this to be helpful, but all patients with rapid respirations must be watched carefully for the first sign of "dusky" of the skin.

The disadvantages of administering oxygen by mask lie in the fact that it may increase restlessness and apprehension. We have used sedatives freely to control

developments, believing that the most important indication was to relieve cyanosis even if this entailed a greater need for sedatives. In the occasional case, oxygen by nasal catheter sufficed to relieve cyanosis and did not disturb the patient as much as the mask. However, in the average case this did not result in high enough concentrations for the abolition of cyanosis.

(b) Blood transfusion. In all, fifty transfusions were given to the 200 patients in the statistical series. The most obvious indications were intestinal hemorrhage, and abnormalities of the clotting mechanism. Another indication was a grave illness with its relatively marked drop in hemoglobin. Half the transfusions given were administered to this group. It was our impression that definite benefit resulted from this therapy. There was never any evidence that, given slowly, it overburdened the circulation, even in the face of cardiac enlargement. Plasma was used only to combat hypoproteinemia.

(c) Heroic sedation. Many gravely ill patients developed a state which we have termed "malignant restlessness." They thrashed around the bed constantly, sat up, attempted to get out of bed, and appeared to be depleting their reserves rapidly. In such cases, barbiturates were usually ineffective. The best results were obtained by rectal paraldehyde, 30 cc. in oil, repeated every few hours if necessary. Although we have no absolute proof of the value of this measure, it was our impression that it was sometimes lifesaving. Rare cases could only be quieted by intravenous sodium amytal, one patient requiring 1.6 grams within an hour.

Morphine was useful in the milder cases, especially when pain was an important factor in their restlessness. It was not used in the presence of any evidence of reduced respiratory function.

Lumbar puncture was done in a number of individuals with headache and stiff neck. Drainage of 15 to 20 cubic centimeters of cerebrospinal fluid appeared to give some relief from pain.

Management of acute myocarditis. No specific therapy was directed at the myocardium. Digitalis was not prescribed because congestive failure did not appear. We felt that our patients were receiving adequate general care for an acute myocarditis because of the routine of absolute rest, the semi-orthopneic position attained by the use of a Gatch frame, the control of restlessness by sedation and of cyanosis by oxygen. Intravenous fluid and blood were given cautiously, for we assumed that every seriously ill patient might have a severe rickettsial myocarditis. However, fluids were never withheld when clear indications for them existed.

(3) *Treatment of complicating infections.* Most of our patients had been exposed to malaria and many had received atabrine and/or quinine before they reached us. We usually continued these drugs, and sometimes ourselves initiated anti-malarial therapy without finding plasmodia in the blood. No untoward effects were observed.

Penicillin or sulfonamide therapy was used in the presence of evidence suggesting a pyogenic complication such as purulent bronchitis, bronchopneumonia, or an acute bacterial meningitis. We never saw any toxic manifestations attend the use of these agents.

b *Therapeutic experiments*

(1) *Penicillin* During the early summer of 1944, penicillin was given an extensive trial, in the hope that it might have some beneficial effects on scrub typhus. Thirty-six patients were treated with total dosages varying from 500,000 to 6,500,000 Oxford Units (the average being 1,500,000). The drug was administered intramuscularly in 25,000 unit doses or more every three hours. Therapy was instituted at almost every stage of the disease from the second to the seventeenth day and in patients of all grades of severity. At first, we were hopeful that some benefit had resulted, but eventually were forced to the conclusion that penicillin did not abort the disease, make its course milder, reduce the incidence of signs of major organ damage in severe cases, nor prevent patients from dying. Furthermore, some patients who had received the drug for many days developed evidences of secondary infection in spite of this therapy, two having pneumococci in their sputum and one having severe purulent bronchitis and bronchopneumonia at necropsy. The possibility of developing penicillin resistant strains in patients who later in their disease might have a real need for bactericidal agents appeared to contraindicate the routine use of penicillin.

(2) *Immune blood and plasma therapy* This form of therapy was not found to be beneficial, but since others may be tempted to try it, our attempt will be described in some detail.

Twenty-two of the first 30 survivors in the statistical series were bled two to five days after their fever had subsided. It was found that even those who had been severely ill tolerated the loss of 500 cc of blood very well. Except for slight pulse rate increases for several subsequent days, there were no untoward reactions. One patient who had only 120 grams of hemoglobin was transfused immediately following venesection. A unit of plasma was administered to the first few donors but was found to be unnecessary. Convalescence did not seem to be retarded by the bleeding.

About 10,000 cc of convalescent blood were thus obtained. The time of venesection was almost always the fourth week of disease although a few patients were bled in the third week. The Weil-Felix titer was usually maximal or beginning to fall. The Proteus OX-K titer varied from 1:50 to 1:200.

Our first three subjects were the second, third and fourth typhus deaths in the series. They were desperately ill when transfused. No untoward reaction appeared to result from the procedure, nor was there any obvious beneficial effect. It was clear that dying patients could not be saved or even temporarily helped by immunotransfusions up to 750 cc (fig 30).

We were then fortunate in receiving a large influx of early cases in the next few weeks. Three of these were selected for immunotherapy. Transfusions were given on the fourth, fifth and sixth day of disease. Our dosage was not massive by some standards. The equivalent of 2000 cc of whole blood was given at most.

The results of therapy in the three survivors were not such as to argue for its effectiveness (fig 30). One patient had an uneventful mild course but showed the usual amount of fever and general illness for this grade of disease severity.

Of the remaining two cases, one had repeated severe reactions to the plasma and then became so ill that his survival was in doubt and he was given penicillin in full dosage. He had "typhus pneumonia", uremia, transient anuria, edema and ascites, and was clearly in the "grave" group. The last patient, #40, ran a typically severe course with high fever, complicated by cardiac enlargement. There is no evidence that the course of these three patients was alleviated by immunotherapy. It was not felt to be worth the while to make further trials of immune blood after our original stock was exhausted.

(3) *Air-conditioning* In June, 1944, after 150 cases of scrub typhus had been treated in this hospital, we were fortunate in obtaining air-conditioned wards for the subsequent 300 acutely ill patients. Although, as figure 1 shows, there was an immediate and dramatic drop in mortality, a multiplicity of factors were operative, making a controlled experiment impossible. The rigors of jungle marching had given place to fixed warfare at the Myitkyina siege and facilities for early medical care and prompt evacuation were available. When jungle combat was resumed in the winter of 1944-1945, the mortality rose once more to

CASE NO	DAY TREATMENT BEGUN	BLOOD	PLASMA	SEVERITY	DURATION OF FEVER	REACTION
		cc.	cc.		days	
33	18	500	0	Mortal	19	None
31	10	0	750	Mortal	12	None
15	16	500	250	Mortal	19	None
46	4	350	900	Grave	18	Rigors
40	4	500	1000	Severe	20	Urticaria
45	4	500	500	Mild	12	None

FIG. 30. RESULTS OF IMMUNOTHERAPY

the level reached in May, 1944 (fig. 1), despite the fact that all cases were treated in air-conditioned wards.

None the less, the value of air-conditioned wards for scrub typhus patients under tropical conditions appeared to be definite. Sweating was reduced and the comfort and morale of the patients improved greatly. The ward staff were required to devote less time to sponging patients and changing bedding and could devote more time to administering food and fluid and to giving general care. Oxygen masks were better tolerated in a cool environment. Thus, although convincing statistical proof was not obtained, we felt that air-conditioning was one of a number of important therapeutic imponderables which might turn the tide in a favorable direction for dangerously ill patients.

### c. The management of convalescence

(1) *Disposition of convalescents* Convalescents were classified into the following groups at the conclusion of the febrile period, on the basis of the temperature chart and the signs of major organ damage during the febrile stage.

*Mild*—less than two weeks of fever, with 104°F. not more than once

b *Therapeutic experiments*

(1) *Penicillin* During the early summer of 1944, penicillin was given an extensive trial, in the hope that it might have some beneficial effects on scrub typhus. Thirty-six patients were treated with total dosages varying from 500,000 to 6,500,000 Oxford Units (the average being 1,500,000). The drug was administered intramuscularly in 25,000 unit doses or more every three hours. Therapy was instituted at almost every stage of the disease from the second to the seventeenth day and in patients of all grades of severity. At first, we were hopeful that some benefit had resulted, but eventually were forced to the conclusion that penicillin did not abort the disease, make its course milder, reduce the incidence of signs of major organ damage in severe cases, nor prevent patients from dying. Furthermore, some patients who had received the drug for many days developed evidences of secondary infection in spite of this therapy, two having pneumococci in their sputum and one having severe purulent bronchitis and bronchopneumonia at necropsy. The possibility of developing penicillin resistant strains in patients who later in their disease might have a real need for bactericidal agents appeared to contraindicate the routine use of penicillin.

(2) *Immune blood and plasma therapy* This form of therapy was not found to be beneficial, but since others may be tempted to try it, our attempt will be described in some detail.

Twenty-two of the first 30 survivors in the statistical series were bled two to five days after their fever had subsided. It was found that even those who had been severely ill tolerated the loss of 500 cc of blood very well. Except for slight pulse rate increases for several subsequent days, there were no untoward reactions. One patient who had only 120 grams of hemoglobin was transfused immediately following venesection. A unit of plasma was administered to the first few donors but was found to be unnecessary. Convalescence did not seem to be retarded by the bleeding.

About 10,000 cc of convalescent blood were thus obtained. The time of venesection was almost always the fourth week of disease although a few patients were bled in the third week. The Weil-Felix titer was usually maximal or beginning to fall. The Proteus OX-K titer varied from 1:50 to 1:200.

Our first three subjects were the second, third and fourth typhus deaths in the series. They were desperately ill when transfused. No untoward reaction appeared to result from the procedure, nor was there any obvious beneficial effect. It was clear that dying patients could not be saved or even temporarily helped by immunotransfusions up to 750 cc (fig 30).

We were then fortunate in receiving a large influx of early cases in the next few weeks. Three of these were selected for immunotherapy. Transfusions were given on the fourth, fifth and sixth day of disease. Our dosage was not massive by some standards. The equivalent of 2000 cc of whole blood was given at most.

The results of therapy in the three survivors were not such as to argue for its effectiveness (fig 30). One patient had an uneventful mild course but showed the usual amount of fever and general illness for this grade of disease severity.



Of the remaining two cases, one had repeated severe reactions to the plasma and then became so ill that his survival was in doubt and he was given penicillin in full dosage. He had "typhus pneumonia", uremia, transient anuria, edema and ascites, and was clearly in the "grave" group. The last patient, #40, ran a typically severe course with high fever, complicated by cardiac enlargement. There is no evidence that the course of these three patients was alleviated by immunotherapy. It was not felt to be worth the while to make further trials of immune blood after our original stock was exhausted.

(3) *Air-conditioning* In June, 1944, after 150 cases of scrub typhus had been treated in this hospital, we were fortunate in obtaining air-conditioned wards for the subsequent 300 acutely ill patients. Although, as figure 1 shows, there was an immediate and dramatic drop in mortality, a multiplicity of factors were operative, making a controlled experiment impossible. The rigors of jungle marching had given place to fixed warfare at the Myitkyina siege and facilities for early medical care and prompt evacuation were available. When jungle combat was resumed in the winter of 1944-1945, the mortality rose once more to

CASE NO	DAY TREAT- MENT BEGUN	BLOOD	PLASMA	SEVERITY	DURATION OF FEVER	REACTION
		cc.	cc.		days	
33	18	500	0	Mortal	10	None
31	10	0	750	Mortal	12	None
15	18	500	250	Mortal	19	None
48	4	350	900	Grave	18	Rigors
40	4	500	1000	Severe	20	Urticaria
45	4	500	500	Mild	12	None

FIG. 30 RESULTS OF IMMUNOTHERAPY

the level reached in May, 1944 (fig. 1), despite the fact that all cases were treated in air-conditioned wards.

None the less, the value of air-conditioned wards for scrub typhus patients under tropical conditions appeared to be definite. Sweating was reduced and the comfort and morale of the patients improved greatly. The ward staff were required to devote less time to sponging patients and changing bedding and could devote more time to administering food and fluid and to giving general care. Oxygen masks were better tolerated in a cool environment. Thus, although convincing statistical proof was not obtained, we felt that air-conditioning was one of a number of important therapeutic imponderables which might turn the tide in a favorable direction for dangerously ill patients.

### c. *The management of convalescence*

(1) *Disposition of convalescents* Convalescents were classified into the following groups at the conclusion of the febrile period, on the basis of the temperature chart and the signs of major organ damage during the febrile stage.

*Mild*—less than two weeks of fever, with 104°F not more than once

*Moderate*—less than three weeks of fever, less than one week at 104°F, and less than three days at 105°F

*Severe*—more fever than Class II or signs of major organ damage

(a) Pulmonary—Respiratory rate of 36 per minute for two days and/or cyanosis

(b) Cardiac—Definite enlargement (apex impulse well to the left of the mid-clavicular line) or a major electrocardiographic abnormality

(c) Central nervous system—Meningoencephalitis, delirium, stiff neck and positive Kernig, focal signs

*Grave*—Life in jeopardy, severe "scrub typhus pneumonia" (prolonged cyanosis) and severe central nervous system involvement (severe delirium, coma or a convulsion)

Patients in the mild and moderate groups were to be returned to full duty

Patients in the "grave" group were to be returned to the Zone of the Interior

The remaining 21 per cent in the severe group were the only cases where the decision was doubtful, and had to be made on the basis of the patient's former duty, and his progress during the convalescent period

(2) *Disposition of these patients was generally carried out as follows* The patient was told, immediately after becoming afebrile, what his probable disposition would be, and from this moment on, his physical and psychological convalescence was managed with this point of view as a background. Those definitely to go to the United States were segregated and sent off as soon as they could travel. The rest were placed in wards under the care of personnel experienced in the management of scrub typhus convalescents, and were guided gently but firmly in the proper direction

The average "mild" or "moderate" patient got out of bed about three days after defervescence, received latrine privileges in a week, and went to the mess hall in ten days. From that time on he progressed through a special reconditioning program, beginning with very mild calisthenics and proceeding gradually to athletics and finally to strenuous marching and running. The whole program took about three or four months in those who were to be returned to combat duty. Each patient was watched carefully and the rate of reconditioning was individualized on the basis of general appearance, weight, appetite, reaction to effort,<sup>2</sup> eyeground findings and the sedimentation rate. If he was pushed too fast he did not do well physically. If he was not kept steadily progressing he was likely to suffer psychologically.

The psychologic reconditioning of these patients was as important as their physical rehabilitation. If the medical officer seemed worried or uncertain, psychiatric symptoms were likely to be exaggerated. If physical reconditioning was pushed too hard and dyspnoea and palpitation developed, the ward officer could readily intensify an "effort syndrome" by listening to the heart, taking the pulse and measuring the blood pressure at frequent intervals.

<sup>2</sup> Exercise tolerance was estimated on the basis of the patient's general appearance after a given amount of exercise, rather than by the so-called "exercise tolerance tests" involving measurements of blood pressure and pulse.

In general it was our policy to pay careful attention to all symptoms which appeared during the first two weeks of convalescence and consider them significant until proved otherwise. If no major complications occurred during that period of time, symptoms which developed subsequently were minimized, unless they were accompanied by significant objective signs. They often became exaggerated if the patient believed that the ward staff was worried about him. With proper reassurance, such symptoms generally disappeared in a few days.

(3) *Results* Of the 472 surviving American cases, the percentage falling into the various severity groups were as follows

Mild	31%
Moderate	42%
Severe	21%
Grave	6%

According to our present standards of convalescent treatment, 75-85 per cent of these should have been able to return to full duty in the theater after an appropriate interval.

Since these standards were not developed and regularly applied until we had studied 172 cases, the results on this first group were less satisfactory. Only 62 per cent returned to their original assignments. Most of the rest were returned to the Zone of the Interior. In retrospect, we find that more than a third of these were "mild" or "moderate" and could probably have been rehabilitated completely. In this "trial and error" group of 175, the incidence of psychoneurosis was high, because of inexperienced management, because of our uncertainty in evaluating neuropsychiatric symptoms, and because of the general impression among the patients that scrub typhus was a disease with dire sequelae.

The remaining 300 cases illustrate the results which may be expected from a coordinated plan of convalescent management.

Eighty-two per cent were returned to full duty, while only 15 per cent, all "severe" or "grave", were reassigned or returned to the Zone of the Interior. Three per cent who were "mild" or "moderate" were also dispositioned to the United States but in every case some cause in addition to the scrub typhus itself was present.

(4) *Summary* The management of scrub typhus in convalescence consists of the following measures:

(a) Careful evaluation of severity of disease by the ward officer who treated the patient, with classification according to the criteria outlined above.

(b) Early decision as to the probable future of the patient on the basis of this classification, and communication of this decision to him, to minimize anxiety and uncertainty.

(c) Segregation of convalescents in special wards with experienced personnel.

(d) Early mobilization, great watchfulness for complications in the first two weeks, and minimizing of symptoms thereafter.

(e) A coordinated individualized physical and psychological reconditioning.

program which avoids equally the errors of pushing the patient too rapidly or too slowly

(f) The use of certain objective signs as minimal criteria for the completion of convalescence general appearance, weight, reaction to effort, disappearance of eyeground abnormalities and the return of the sedimentation rate to normal

## 8 SUMMARY

In a clinical study of 616 cases of scrub typhus, we have presented a general picture of the disease, differentiating the mild and moderate illnesses which carried no significant mortality from severe and grave infections with a mortality of 25-50 per cent

Clinical variations were presented with 200 consecutive cases as a basis for statistical analysis, amplified by the experience derived from the entire group, together with certain fundamental laboratory findings and a discussion of differential diagnosis

Clinicopathologic data on major parenchymal organ dysfunction in dangerous and mortal illnesses were given with their diagnostic criteria and prognostic significance and correlated with chemical, roentgenologic and electrocardiographic findings

The complications and sequellae to be expected in convalescence were described

An outline of the therapy and management of the acute disease was given, together with the results of certain therapeutic experiments and a report on our experience with the problems of convalescent management and disposition in the India-Burma Theater of Operations

Acknowledgment is made of the contribution to this study of the following

- (1) 1st Medical Museum and Arts Detachment for the photography and drawings
- (2) Calvin F Kay, Major, M C , and Horace H Hodges, Captain, M C , Ward Officers on the Typhus Wards
- (3) Brigadier General Isidor S Ravdin, without whose continued interest and help the adequate study and care of the cases would not have been possible

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# CLINICAL AND THERAPEUTIC ASPECTS OF THE CONFLAGRATION INJURIES TO THE RESPIRATORY TRACT SUSTAINED BY VICTIMS OF THE COCOANUT GROVE DISASTER<sup>1</sup>

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<sup>1</sup> The work described in this paper was done in part, under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University

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In their comprehensive report on the Management of the Cocoanut Grove Burns at the Massachusetts General Hospital, Cope and others (1) recounted their experiences with the victims of that holocaust. Many of the problems which confronted the workers at the Boston City Hospital, both on the night of the disaster and throughout the hospital stay of the patients, were strikingly different from those encountered at the Massachusetts General Hospital. The type of personnel, the number of cases, the facilities and arrangements for their care, the methods of approach and the details of almost every phase of their management were decidedly different at the two institutions. A record and discussion of some of the experiences at the Boston City Hospital, are, therefore, amply justified even at the risk of a certain amount of repetition. A number of studies made in these cases have already been published (2-12) or will appear in due time (13-15). The present report deals primarily with the clinical aspects and management of the respiratory complications and with certain other medical features of those victims of the Cocoanut Grove fire who were alive at the time of admission to the Boston City Hospital.<sup>2</sup>

#### THE COCOANUT GROVE NIGHT CLUB FIRE, NOVEMBER 28, 1942

A brief account of the fire may serve to bring the present report into its proper perspective and may be particularly helpful for the understanding of the nature and possible causes of the respiratory complications. The report of Robert S Moulton (16), prepared for the National Fire Protection Association six weeks after the event, gives the facts of the fire insofar as they could be determined from all sources available to him at that time. Excerpts relevant to the subject matter at hand will be quoted from that report, with the permission of its author.

<sup>2</sup> The general administration of the study and management of the cases as well as the details of the surgical features were under the direction of Dr Charles C Lund who, at the time of the disaster, was the responsible investigator in a study of burns at the Boston City Hospital. The biochemical and physiological studies were carried out by Dr F H L Taylor and his staff as part of these studies. It is to them and to the members of the visiting and resident staffs of the Boston City Hospital that the present authors are chiefly indebted for the opportunity to make the observations recorded here. The pathological and medico-legal studies were conducted by Dr Timothy Leary, Chief Medical Examiner for Suffolk County, and his associates. Dr Leary's careful and painstaking pathological observations were of the greatest help in clarifying the difficult clinical problems presented by the severe respiratory tract complications with which we are chiefly concerned in the present report. The special problem arising out of the finding of hemoglobinuria in a number of severely burned cases was studied and reported by Doctors T H Ham and S C Shen (10) and the neuropsychiatric features were studied chiefly by Dr Alexandra Adler (11, 12). Needless to say, numerous other members of the hospital staff as well as others contributed voluntarily and generously of their time and skills both for the care of the patients and in the study of the problems which they presented.

"The Coconut Grove was a typical night club. The building was crowded to capacity on the Saturday night after a football game. No exact figures are available, but it appears that the number was about 1,000 as compared with a reported official seating capacity of something over 600. Gaiety was at its height, the several bars were crowded, tables around the bars were filled to capacity with every available square foot of floor space occupied. The show was about to begin soon after 10 p.m.

"Fire started in the Melody Lounge, a basement cocktail lounge. Feeding on the highly combustible decorations, artificial cocoanut palms and cloth-covered ceilings and walls, it spread with great rapidity. The fire spread up the stairs from the Melody Lounge cutting off the only viable means of exit. The people on the main floor had no warning of impending tragedy. Some of the surviving witnesses said the first they knew of the fire was when a girl with blazing hair ran screaming across the room. Others first saw flames flashing through the air just below the ceiling. There was a mad rush for the exits. The main doorway (the Piedmont Street exit), which was the only exit that most of those present knew, was blocked by a revolving door which quickly jammed and some 200 of the victims were piled up behind it. The flames also flashed through a corridor to the Broadway Cocktail Lounge and here 100 victims piled up behind a door swinging the wrong way which blocked access to the outside doorway. A door leading to Shawmut Street was partially opened by an employee, but other doors were locked. A few people escaped from the basement by crawling out of a small cellar window. Some escaped through the small windows of the toilet rooms. A few made their way up the stairs to the second floor dressing rooms in the converted tenement building that formed the Broadway end of the club and got out through windows onto roofs. It will probably never be known just where in the building all of the victims perished and just how many made their exits through windows and over the roof. So rapid was the travel of the fire and the noxious smoke and gases that many apparently collapsed at their tables without even making a move toward the exits.

"The fire department was on hand immediately, opened doors, broke in windows and rescued as promptly as possible all the victims who were still alive. The windows of the building were completely obscured from the inside except for the glass block windows on the Broadway side and the fire department was somewhat delayed in gaining access. In general, however, the occupants were in complete ignorance of the possible means of emergency exit. With many of the doors locked, and with such a fast-spreading fire, accompanied by noxious fumes, it is doubtful whether complete knowledge of the arrangement of the building would have resulted in saving any large number of lives.

"There was a great deal of drinking and this may have befogged some of the victims, creating conditions more than usually conducive to panic. We cannot believe, however, that the presence of liquor was any material factor in the loss of life.

"When the cry of "fire" was raised in the Melody Lounge most of the occupants appear to have rushed for the stairway which presented the only obvious exit. This stairway led to a narrow hallway on the first floor which in turn emptied into a foyer passing the check room and leading to the main entrance. Had not the door leading to the street from the hallway at the head of the stairs from the Melody Lounge been locked, a much more direct means of exit would have been available. This locked door undoubtedly was responsible for many fatalities. Persons escaping from the basement were unable to pass into the street but were piled up in the corridor and foyer while attempting to reach the main exit. A number of persons even failed to reach the first floor. Rescue workers removed a number of bodies and several still living persons from the basement. Apparently a few persons made their escape from the lounge by going to the kitchen section. Some of these guests and employees attempted to escape by means of stairways to the main floor but found that escape by that route was impossible because of the heat of the main floor. A few persons escaped through a basement window into a courtyard and a few others survived the fire by seeking refuge in a large refrigerator.

\* A floor plan is shown in figure 1

"All accounts agree that the flames flashed into the main floor a very few moments after the outbreak of the fire. It is reported that some persons lost their lives before they had an opportunity to escape from the tables where they were seated. Reports indicate, however, that some of the persons who attempted to leave at the first indication that a fire was in progress in the basement made good their escape. Others who delayed even momentarily or who started for the checkrooms to obtain their wraps, were caught in the rush for the exits when the magnitude of the fire became apparent. It was reported by some witnesses that the electric lights failed early, but in the confusion they may not have distinguished between failure of the lights and dense smoke obscuring the normally dim illumination.

"Several persons who escaped from the main dining room reported that flames appeared to roll through the air rather than spread along the surface of the ceiling. Flames quickly swept through the passageway into the new cocktail lounge off Broadway.

"It is reported that perhaps 100 of the fatalities occurred behind the Broadway entrance more than 190 feet distant from the stairway leading from the basement lounge where the fire started. In addition to those who succumbed inside the building, a considerable number died after removal from the building due to severe burns and lung injuries resulting from the effects of heat and fire gases.

"Boston hospitals learned of the disaster about 10 30 p m when their accident admitting wards were suddenly faced with stretcher bearers bringing casualties into the wards and when police calls came in requesting ambulances and personnel to come to the fire. In this way, activation and mobilization of the hospital organizations set up under civilian defense for handling air raid casualties occurred from two sources and got under way promptly. Non-resident staff was notified to report through a predetermined and posted fan-out schedule. All leaves for hospital help were cancelled. Upon notification by radio, doctors from 30 miles around Boston and medical students from Great Boston colleges reported. More than 200 of the Navy's medical personnel treated survivors and rescuers, both civilian and military. Medical authorities from all over the nation wired offers of help.

"Victims who escaped quickly either went unaided or were sent by police to hospitals in taxis. The streets were choked with fire-fighting equipment and vehicles trying to get victims to the hospitals. Many expired en route to hospitals. The Mortuary service by 1 30 a m had over 400 bodies accounted for in the various morgues throughout the city.

Four hundred and eighty-nine persons lost their lives in the fire on the evening of November 28, 1942.

"The Field Casualty Service of the Civilian Defense Emergency Medical Service of the City of Boston pivots primarily on eight of the city's general hospitals (which) have a total casualty capacity of 876. Facilities for 181 Cocoanut Grove victims were required.

Observers at the Boston City and Massachusetts General Hospitals, which received more than 80 per cent<sup>5</sup> of the casualties, reported that everyone did his duty efficiently and effectively.

"It was estimated that one Cocoanut Grove fire victim reached the Boston City Hospital every 11 seconds, which is a faster rate than casualties were taken to any hospital during London's worst air raids. The Boston Metropolitan Chapter of the American Red Cross mobilized more than 500 workers within 30 minutes after being routinely alerted.

As the horribly burned victims crowded hospitals, the Nurses Aides Corps mobilized nearly 500 aides to relieve overworked regular hospital staffs and the nursing service mobilized close to 300 volunteer nurses for the emergency services of the first few days. Later, more than 100 trained nurses were assigned to duty, at Red Cross expense, to help carry the burden of caring for the injured."

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<sup>4</sup> At least 3 others are known to have died as a result of the fire subsequent to the date of Moulton's report.

<sup>5</sup> Actually these 2 hospitals received, on the night of the fire, 94 per cent of this total of living casualties, 131 being admitted to the Boston City Hospital and 39 to the Massachusetts General Hospital. The problem as it confronted the latter hospital has already been described (17).



ADMISSION, DISTRIBUTION AND EARLY CARE OF THE CASES BROUGHT TO THE  
BOSTON CITY HOSPITAL

A few pertinent facts concerning the events as they transpired on the night of the fire will be mentioned briefly in order to picture roughly the situation which confronted the physicians at that time. These facts may help to understand and to evaluate the problems to be discussed.

The admitting floor of the Boston City Hospital, as may be expected of the only large public hospital in a Metropolitan area, is always a busy place on Saturday nights. Its facilities are usually well occupied on such nights in caring for the few patients who come to receive emergency treatment for injuries and in processing the sizeable number of patients brought there by ambulance, police cars, taxicabs and private cars or arriving on foot for admission to the wards. Often they are accompanied by a number of relatives, friends, police officers, newspaper reporters and others anxious to give or acquire information and assistance. The early evening of November 28 before the time of the fire was just another Saturday night on this floor until about 10:30 p.m. when vehicles of all descriptions began discharging the casualties from the Coconut Grove at an ever increasing rate.

The first few patients were handled in the routine manner and then sent to operating floors or shock rooms as was customary for such cases. It was not long, however, before the magnitude of the emergency was fully appreciated and the examining rooms, corridors and waiting rooms were literally filled with dead and dying and with a large number of living who had burns of varying extent and severity. By this time, mobilization of the hospital personnel was well under way. The entire resident staff of doctors, nurses, and attendants was immediately pressed into service and members of the visiting staff began to appear in increasing numbers after being summoned according to a plan previously arranged for use in case of air raid emergencies. Many others came of their own accord on hearing of the tragedy or in response to calls by the various agencies already mentioned. They were dispatched to the operating rooms and to the various parts of the hospital with the patients to render whatever assistance should be required by the regular hospital staff.

Two wards especially equipped to receive disaster victims were soon opened and were rapidly filled to overflowing with patients. The other casualties were sent to any surgical or medical wards where beds were available. In less than 3 hours the dead had been segregated and delivered at the mortuary and 131 casualties had been distributed in 31 wards in 8 different buildings located in all parts of the main hospital. With the patients, in each of the wards where more than 1 or 2 patients had been sent, there came staff members, nurses and many others, most of whom helped in every possible manner to care for and comfort the patients. To these were often added relatives, friends and others who were at the bedsides or filled the corridors and kept inquiring frequently about the condition of the patients. Many physicians on finding the patients adequately cared for left or went to other wards, while others lingered to observe and some returned frequently to follow the progress of the cases.

In general, the only therapy carried out on the admission floor was the routine injection of morphine to each of the victims, and administration of plasma was begun in the first few cases on the operating floor. For the most part, however, the patients received plasma and other therapy on the wards. Treatment of the surface burns by a number of surgical teams began early in some of the first few cases but later the efforts of most of those present were directed to the emergency problems of preventing shock and relieving restlessness, pain and discomfort, leaving the surface treatment for the earliest opportune time.

Before the majority of the patients had been admitted, some of those who were just being brought in and others who were already on the various wards began to manifest signs of severe respiratory distress. Shortly thereafter some of the patients showed definite evidence of obstruction to the air passages which required rapid mechanical relief and deaths began to occur either in spite of these efforts or before much could be done. Members of the Aural Service of the hospital soon appeared on the scene and were constantly present to carry out laryngoscopies, tracheal suction and tracheotomies.

A great deal of effort on the part of many of the persons who first saw the victims on arrival was expended in vain attempts to keep alive or resuscitate a few who were obviously dying. Most of these soon died in the admitting room and are not included among the hospitalized cases. One, a recent intern at this hospital, was picked out from among those considered to be dead when he was seen to give one gasp and after vigorous and prolonged artificial respiration and stimulation was resuscitated but remained comatose in spite of intensive therapy until he died 30 hours later.

As might be expected from what has already been said, much of what transpired on the admission floor and on the wards during the first few crucial hours was not adequately recorded at the time. In a number of cases details were later obtained from those who observed the patients. On most of the wards notes were kept at the bedside of each patient and the therapy prescribed and carried out were thus recorded together with brief notations by doctors and nurses on the condition of the patient in many instances. At the height of the excitement and under the pressure at the time many details did not get recorded. In particular, notes on the physical findings in individual cases during the first few hours are scant although most of the patients were examined by a number of observers.

The observations made by the physicians who saw the patients first, that is, by those who were on the admitting floors at the time, are of the greatest interest in evaluating the later course of the patients in the hospital and they are also of importance in interpreting the nature of the respiratory lesions. Unfortunately most of these observations were not recorded. However, a brief summary of an account of some of the events that transpired on the admitting floor may be of interest. These are taken from a report which was obtained from one of the interns who was on duty on the accident floor from the time when the first patient was received.<sup>6</sup>

<sup>6</sup> We are indebted to Dr Crawford Adams, intern on the Fifth (Boston University) Medical Service for this account.

"The first news of the disaster was received when three male patients came running into the Admitting Floor with hands and face covered with first and second degree burns. They stated that there was a large fire at the Coconut Grove and that there were many casualties. Immediately the male nurses and orderlies were instructed to clear two rooms of patients already on the Admitting Floor to prepare to receive the injured. Another nurse was asked to prepare morphine and to give 15 mg to each of the patients on arrival. The three patients were placed on litters, their coats removed and placed over their bodies and these covered with blankets.

"Within a few minutes both of the rooms were filled with new arrivals. At this time all admitting rooms were ordered cleared and an emergency call was issued for all House Officers and resident hospital personnel. The proper authorities were notified of the magnitude of the disaster.

"The first House Officers to arrive within five minutes were asked to help in the administration of morphine. The drug was prepared in 20 cc syringes with tap water so that each cc contained gr  $\frac{1}{4}$  (0.015 gm). Each patient on the floor was immediately given morphine gr  $\frac{1}{4}$  and marked with an 'M' in lipstick on the left anterior chest wall. Two interns were then stationed at the entrance to the Admitting Floor and as the living patients entered they were given morphine gr  $\frac{1}{4}$  subcutaneously and similarly marked. Two others were stationed at the entrance and they pronounced those patients who were dead on arrival. The dead bodies were temporarily placed aside and the living patients permitted to enter the floor. Within thirty to forty five minutes after the arrival of the first few patients the entire Admitting Floor and corridors were filled with patients. Many of these were dying or dead.

'From the clinical standpoint the cause of death appeared to be chiefly asphyxia. Most of the dead had first and second degree burns of face, hands, upper extremities and in many cases of the anterior chest wall, but the majority of the living ones had minimal burns. Many of the burned areas were covered with a great deal of black soot. A few of the dead had a bright "cherry red" color of their mucous membranes and lips which clinically suggests carbon monoxide poisoning. The majority of the dead had edema of the face, neck and oral structures. A few patients who were apparently comfortable at first glance soon began to cough up frothy sputum and then expired. Two or three other patients who clinically showed respiratory distress, upon physical examination had diffuse, generalized moist rales and rhonchi throughout both lung fields. These cases had minimal first and second degree burns of face and extremities.

'Of the living patients, the majority were calm and behaved extremely well. A few complained of their burns and some became hysterical but quieted down after vigorous psychotherapy. One of the male patients who was about twenty years old, was disoriented and appeared intoxicated. There were only about ten living patients with severe generalized burns who died on the admitting floor. Two of them had almost their entire bodies burned and became extremely restless, irrational and delirious. Both of them were given morphine gr  $\frac{1}{4}$  in addition to the gr  $\frac{1}{4}$  on entrance. The seriously burned patients who, from a clinical viewpoint were not in shock, were transported directly to the operating floors for treatment of their burns. Within about an hour and a half after the arrival of the first patients the corridors and majority of rooms were cleared of patients."

The details of the way the patients were handled during the first few hours obviously varied considerably from ward to ward. A first hand account of the events as they transpired on one of the special casualty wards will serve to picture the situation on the night of the fire. A senior member of the Nurses' Training School Staff had been dispatched with 5 pupil nurses to open this ward for the reception of casualties, and a number of physicians had been delegated to attend these patients. One of the authors (C S D) who arrived on the admitting floor at 11 15 p.m. was taken directly by Dr Lund to this

ward and left to take general charge of the patients there. By that time 15 patients had already been received and bedded, and 3 additional patients arrived by midnight.

One of the nurses was promptly detailed to go from bed to bed and to take and record the pulse and respiratory rates and the blood pressure on each patient in rotation. Three of the nurses were assigned to the special nursing care of the sicker among the patients, each being asked to care particularly for one of the 3 sickest patients (Cases 100, 102, and 110). Many of the details of the nursing care were carried out by the interns and by the other physicians present. Since there was no plasma and very little in the way of sterile solutions for parenteral injections on the ward, the remaining pupil nurse was dispatched with the ward truck to obtain these materials from the solutions room and to gather up some sterile supplies from the operating floor.

A quick inspection of the patients was then made. One of the striking features of the ward was the strong odor of smoke and the pungent odor of charred flesh which permeated the entire ward and was accentuated as one approached the most severely burned victims. Several with extensive burns were found to be in shock. One of these patients (Case 102) had severe burns of all exposed surfaces and of the entire back. She was lying on her abdomen and on casual inspection was thought to be a dark skinned negress but on closer observation she was seen to have charred skin which gave the impression of pigmentation. Three of the patients showed only slight respiratory difficulty and only minor surface burns of the face and nose but they were also found to have burns of the mouth, pharynx, and nose. One of the latter patients soon developed respiratory distress which increased gradually during the next 6 hours. One of the victims who had severe and extensive burns involving about half of his body surface had similar but more severe respiratory embarrassment. The remainder of the patients showed varying degrees of burns and respiratory difficulties.

Morphine was given freely to those with pain from severe burns. It was also given at first to some of those with severe respiratory distress until one of the patients (Case 63) manifested evidence of definite depression of respiration presumably resulting from an overdose of this drug.

Little or no surface treatment of the burns was attempted at first except for the application of saline or dry dressing wherever this could be done conveniently.

The first supply of plasma arrived on this ward shortly after midnight. It was given first to those severely burned patients who were obviously in shock. It soon became apparent that even some of the patients with less extensive burns, particularly those with respiratory difficulties were developing a steadily increasing pulse rate, falling blood pressure or both. They were also given injections of plasma in the effort to prevent or combat clinical shock. It was considered possible that pulmonary edema also would be prevented or minimized by this procedure. Interestingly enough, no signs of frank pulmonary edema were seen in any of these patients. Also, no engorged cervical veins were seen to suggest any marked increase in venous pressure.

Early in the morning two Naval medical officers assigned to the Department of Physical Chemistry at the Harvard Medical School appeared on the ward with a limited supply of human albumin. This was given by them or under their direction to selected patients who were in the most profound shock. Both of these officers were very helpful in suggesting and carrying out emergency procedures and in following the course of the patients.

Oxygen by the only method available on this ward, namely, by nasal catheter, was begun in the early morning hours. It was started first on those with the severest respiratory distress and was then given to all who manifested respiratory symptoms however mild. No definite benefits from this therapy were noted.

At about 3 a m. two surgical teams appeared on the ward and proceeded to carry out surface treatments (4) on all patients, one by one.

At the time the patients were first sent to the wards, or at least by the end of

the first day, they were each assigned to one of the surgical services. This was done more or less in rotation according to the established custom of the hospital. A few were assigned to medical services either because they were already on their wards and being cared for by their staffs or because the patients had little or no surface burns requiring extensive surgical treatment. In this manner the patients on the special emergency wards were gradually distributed among the regular wards by the various services as soon as beds became available and the condition of the patients permitted.<sup>1</sup>

From what has already been said it is obvious that complete control and direction of every phase of the medical problems in all cases was physically impossible. Many of the important emergencies had to be coped with immediately and by any authorized member of the service who was present near the bedside at the time. Many senior and junior members of the visiting medical staff and the interns and residents of the various medical services and a few outsiders were on hand on all the wards both on the night of the disaster and on the following day or two and helped in every way possible to cope with these emergencies. During the first few hours they were engaged mainly in administration of plasma, fluids and oxygen and in other ways attending to the comforts of the patients. Many of the earliest notes on the physical findings and course of some of the patients were recorded by them.

In order to discharge the medical functions as efficiently as conditions permitted and at the same time avoid conflicts and duplications, a definite procedure was soon adopted. The present authors as a team visited each patient at least once a day and the sickest ones and those of special interest were seen more often, when indicated and feasible, by one or more members of the team. At these visits each patient was examined as thoroughly as seemed indicated and notes were made. All aspects of therapy and nursing procedures carried out since the previous visit were reviewed. Particular attention was paid to the fluid balance and to the details of nursing procedures particularly as they concerned the respiratory complications and chemotherapy. At the same time arrangements were made to obtain materials for such laboratory tests as seemed indicated for the conduct of therapy and for the various studies that were being conducted by Dr F H L Taylor and his associates. It was during one of the earliest of these visits that a specimen of dark colored urine suspected of containing hemoglobin was seen and this formed the basis of the studies by Dr Ham and his associates (10). Recommendations for therapy were then made to the

<sup>1</sup> Responsibility for the conduct and care of each case was thus vested in the visiting staff of one of the hospital services and exercised with and through its residents and interns. Specific surgical problems or special cases from all services, however, are at times "assigned" to designated members of the staff who are then permitted to direct, carry out or study certain phases of their treatment. The management of burn cases had been assigned to Dr C O Lund and his associates. It was at their request and with the consent of the surgeons in charge of the cases that the general supervision over the management of the respiratory complications and of the chemotherapy in the Coconut Grove cases was delegated to the present authors on the morning after the fire.

members of the service in charge of the case and they almost unanimously cooperated most heartily in carrying them out and in bringing them in harmony with those of their own visiting staff and of other members of the burn team who also visited these patients regularly

#### CLASSIFICATION OF THE RESPIRATORY TRACT COMPLICATIONS

Since most of what follows concerns the respiratory tract involvement, a classification of the severity of this complication is desirable chiefly for convenience in presentation. In a general way, all parts of the respiratory tract from the nose and mouth down to the alveoli were involved in certain cases, and even the pulmonary vessels and interstitial tissues were affected in some instances. A classification based on the extent and degree of the pathological changes would, of course, be more desirable, but this obviously is not possible except in the fatal cases in which the respiratory damage was necessarily the most severe. However, the clinical manifestations, including both the symptoms and the physical signs, were the most important from the point of view of the management of the cases. These were classified in a general and more or less arbitrary manner into the following grades according to the severity of the respiratory tract involvement

<i>Grade</i>	<i>Clinical Manifestation</i>
0	No abnormal physical signs or symptoms of respiratory tract damage
1	Signs or symptoms limited to the upper respiratory passages, including mild laryngitis if not accompanied by stridor, cough or sputum. No abnormal physical signs in the lungs or only transient rales
2	Any of above with physical signs suggesting involvement of trachea, bronchi, or of pulmonary parenchyma persisting for 24 hours or longer (except frank signs of consolidation) and accompanied by mild dyspnea without stridor
3	Any of above with moderate or severe dyspnea, cyanosis, wheezing accompanied by transient or intermittent stridor or with frank signs of consolidation
4	Any of above with signs of extensive pulmonary involvement and/or severe stridor with evidence of obstruction to airways necessitating tracheotomy or resulting in death from asphyxia

The changes noted in the X-rays of the lungs were graded independently. For this purpose the extent and degree of the abnormal densities noted in the roentgenograms were graded on a scale from 0 to 4. This proved to be a relatively simple task as compared with the classification based on the clinical data. The details of the X-ray changes are discussed elsewhere (13).

#### RELATION BETWEEN THE SURFACE BURNS AND THE RESPIRATORY DAMAGE

The impression was gained, as the patients were being observed during the first few days, that there was little or no correlation between the extent of the respiratory damage or the severity of the symptoms resulting from this injury on the one hand and the extent and severity of the surface burns on the other. This observation was also made by the workers at the Massachusetts General Hospital (18) where only 3 of the 39 patients admitted from this fire were wholly

free of respiratory symptoms and each of them had covered his mouth with a wet cloth or some article of clothing. Closer analysis of the cases observed at the Boston City Hospital, however, shows a fairly good correlation between the extent of the surface burns and the respiratory symptoms. As seen from table 1, more than three-fourths of the patients who were entirely free from respiratory symptoms had either no burns at all or their burns involved only 4 per cent or less of their body surface. The same was true in about one half of the cases in which there were only moderate symptoms of respiratory tract injury (Grades 1 and 2) and in about one-fourth of those with the severest grades of respiratory involvement. Conversely, about one half of the patients who were entirely free from surface burns were also free from respiratory symptoms, about one-fourth of those with burns involving 4 per cent or less of the body surface were

TABLE 1

*Correlation of the severity of the respiratory involvement and the extent of the surface burn*

BURN % OF BODY SURFACE	A. NUMBER OF CASES						B. % OF CASES WITH VARYING GRADES OF RESPIRATORY DAMAGE			C. % OF CASES WITH VARYING EXTENTS OF SURFACE BURNS			
	Grade of severity of the respiratory involvement												
	0	1	2	3	4	Total	0	1-2	3-4	0	1-2	3-4	Total
0	8	5	0	1	3 <sup>2</sup>	17 <sup>2</sup>	33	10	7	47	30	23	100
1-4	11	13	7	8	3 <sup>2</sup>	42 <sup>2</sup>	46	38	20	26	48	26	100
5-9	4	8	6	6	8 <sup>6</sup>	32 <sup>6</sup>	17	27	26	12	44	44	100
10-19	0	2	2	2	5 <sup>6</sup>	11 <sup>6</sup>	0	13	20	0	40	60	100
20-29	0	2	1	1	3 <sup>2</sup>	7 <sup>2</sup>							
30+	1 <sup>1</sup>	3 <sup>1</sup>	3 <sup>3</sup>	7 <sup>7</sup>	8 <sup>8</sup>	22 <sup>28</sup>	4	12	28	5	27	68	100
Total	24 <sup>1</sup>	33 <sup>1</sup>	19 <sup>8</sup>	25 <sup>7</sup>	30 <sup>27</sup>	131 <sup>38</sup>	100	100	100				

\* The superscripts represent the numbers of fatal cases included

similarly free from damage to the respiratory tract and a much smaller proportion of those with more extensive burns completely escaped having respiratory symptoms. On the other hand, the severe grades of respiratory damage (Grades 3 and 4) were found in only one-fourth of the patients in whom burns were absent or involved 4 per cent or less of the body surface and the percentage of cases with such severe grades of respiratory involvement increased with the extent of the surface burn.

The fatal cases are of special interest. In every fatal case either the respiratory damage was very severe (Grade 4) or the burns were very extensive and involved 30 per cent or more of the body surface. In most of those with burns of less extent the death was attributable chiefly, if not solely to the respiratory complication.

Thus it appears that while there were wide discrepancies between the extent of the surface burns and the severity of the respiratory damage in a number of

individual cases, there was a closer correlation between these two kinds of injuries in most instances<sup>8</sup>

#### CLINICAL FEATURES OF THE RESPIRATORY TRACT COMPLICATIONS

For a clearer picture of the respiratory tract complications in the patients admitted to the Boston City Hospital from the Cocoanut Grove fire, it is best to consider the clinical features of the cases in groups according to the severity of the symptoms. The extent of the surface burns is listed in table 1, most of the relevant clinical details in each group are listed in table 2 and certain features of the exposure to smoke and flame in individual cases are given in table 6. The findings in each group will be summarized briefly and only a few of the most interesting details bearing on these findings in individual cases will be noted.

#### *Cases without definite respiratory tract involvement*

There were 24 patients who were essentially free of symptoms of respiratory complications. One-third of them was also entirely free of surface burns, 1 patient had 8 per cent, 3 had 5 per cent and the rest, with one exception, had 3 per cent or less of their body surface burned. The exceptional case, Number 128, was that of a bartender in the New Cocktail Lounge. He saw the dark gray fumes rush in through the narrow passageway from the Main Dining Room, and after inhaling a small amount of this "strong and bitter smoke which hurt his nose", immediately covered his face with the wet bar rag which he was then holding in his hand. As this patient attempted to reach the exit he was stampeded and fell to the floor face down. His clothes then caught fire and he sustained severe burns of his scalp, neck, extremities and entire back, a total of 30 per cent of the body surface. This patient and one other, Case 74, who

<sup>8</sup> It is of interest to compare these findings with the ones reported in the protocols of the cases admitted from this fire to the Massachusetts General Hospital (1). With respect to the respiratory involvement it is possible, from those brief protocols, to grade the cases only roughly according to the classification set up here. Considering the small numbers involved the distribution of cases according to severity was remarkably similar at the two hospitals. By the classification used here the Massachusetts General Hospital cases would be distributed as follows: Grade 0, 4 cases or 10%, Grades 1 and 2, 17 cases or 43%, and Grades 3 and 4, 18 cases or 46%. These compare with 18%, 40% and 42%, respectively at the Boston City Hospital. As to burns, the distribution of cases according to the per cent of the body surface involved was also quite similar at the two institutions, but with two notable exceptions. While the proportion of cases with burns involving 10 per cent or more of the body surface was quite comparable (17 cases or 44% at the M G H as compared with 50 cases or 38% at the B C H), the proportion of the severest burns, namely those involving 30 per cent or more of the body surface, was greater here (3 cases or 8% at the M G H as compared with 22 cases or 17% at the B C H). Of the patients in the latter category only 1 survived at the M G H and 2 at the B C H. Furthermore, 19 patients were discharged or transferred to other hospitals alive and in good condition within the first 18 hours. Only one of these 19 patients had burns involving 6 per cent of the body surface, 12 had burns involving 3 per cent or less and 6 were entirely free of surface burns. Only 5 of these 19 patients had any respiratory symptoms or positive X-ray findings, either before leaving the hospital or, as far as could be ascertained, at the hospitals to which they were transferred.



TABLE 2

*Summary of the salient clinical features of the respiratory complications observed among the victims of the Coconut Grove fire*

CLINICAL FEATURES (SEE ALSO TABLE 1)	SEVERITY OF RESPIRATORY COMPLICATION (GRADE)					Total
	0	1	2	3	4	
Number of cases	24	33	10	25	30	131
Fatal cases	1	1	3	7	27	39
Condition on entry and first few hours						
Good	20	21	4	3	0	48
Fair	4	10	13	11	4	42
Poor	0	2	2	11	26	41
Evidence of smoke inhalation						
Slight	10	20	5	3	—	38
Moderate or considerable	2	10	13	22	18	65
State of consciousness						
At fire						
Conscious	21	25	11	3	0	60
Unconscious	3	8	8	21	22	62
At entry						
Conscious	24	31	17	18	9	99
Unconscious or stuporous	0	2	2	7	21	32
Shock	1	2	3	10	14	30
History of previous respiratory disease, Total	7	28	13	20	6	74
Acute infection within 2 weeks	0	7	2	2	3	14
Chronic or recurrent infection						
with recent symptoms	0	2	2	4	1	9
without recent symptoms	2	4	0	4	0	10
No recent respiratory infection	5	15	9	10	2	41
Symptoms						
Restlessness	3	0	10	22	26	69
Vomiting	1	10	9	18	19	55
Chills	1	5	4	6	2	18
Hoarseness	0	17	17	21	25	80
Cough	6	26	10	22	27	100
Sore throat	0	5	0	11	6	23
Dyspnea	0	6	11	21	30	68
Cyanosis	0	0	1	6	12	19
Wheezing	0	1	1	10	15	27
Stridor	0	0	2	15	26	43

TABLE 2—*Concluded*

CLINICAL FEATURES (SEE ALSO TABLE 1)	SEVERITY OF RESPIRATORY COMPLICATION (GRADE)					
	0	1	2	3	4	Total
Physical signs						
Nasal burns (internal)	0	10	8	14	9	41
Pharyngeal burns	0	2	2	4	3	11
Musical râles (diffuse)	0	10	11	19	27	67
Crepitant râles (mostly at bases)	0	23	17	23	28	91
Diminished breath sounds	0	3	5	14	4	22
Consolidation	0	0	0	5	2	7
Number of cases with roentgenograms	16 <sup>1</sup>	26 <sup>2</sup>	26 <sup>2</sup>	11 <sup>5</sup>	8 <sup>5</sup>	87 <sup>15</sup>
Pulmonary changes by X-ray						
Grade 0	8 <sup>1</sup>	2	0	0	0	10 <sup>1</sup>
1	8	14 <sup>1</sup>	6	0	0	28 <sup>1</sup>
2	0	8 <sup>1</sup>	8	1 <sup>1</sup>	0	17 <sup>2</sup>
3	0	2	10	7 <sup>1</sup>	1 <sup>1</sup>	20 <sup>2</sup>
4	0	0	2 <sup>2</sup>	3 <sup>3</sup>	7 <sup>4</sup>	12 <sup>9</sup>
Sputum						
Mucoid and scant	0	12	11	13	15	51
Black with soot	0	10	5	8	8	31
Blood-streaked or bloody	0	4	3	11	6	24
Purulent	0	2	4	5	2	13
Hemoglobinuria	0	3	0	5	6	14
Fever (100°F or higher) during first 4 days						
Present on first day	4	10	12	15	20	61
Appeared after first day	3	14	4	6	2	29
Maximum temperatures						
100 or 101°F	5	14	6	6	6	37
102 or 103	2	9	10	11	8	40
104 or 105	0	1	0	1	4	6
106 or higher	0	0	0	3	4	7
Vital capacity during hospital stay						
Day 12						
Number tested	4	12	10	15	1	42
Number with low values	0	7	4	11	0	22
Day 23						
Number tested	1	3	3	7	0	14
Number with low values	0	1	1	4	0	6

Superscripts denote numbers of fatal cases included

sustained burns of the right hand and forearm, were the only ones in this group in whom burns of any part of the body surface were present without the face being involved<sup>2</sup>

Three patients in this group, two of whom had no surface burns, sustained injuries in their attempt to escape from the building. Two of them had contusions, one of the chest and the other of the forehead and other parts of the body, where they were trampled and kicked about, and the third sustained a fracture of the tibia when he tripped over a fire hose.

All of the patients in this group either succeeded in escaping from the building under their own power or were among the first to be extracted. There were 12 among them, however, who recalled having seen smoke and inhaled some of it. Two of these patients, Cases 31 and 85, lost consciousness for a brief period after inhaling what they considered to be a large amount of smoke. Case 85, was a fireman who had "collapsed" in a similar manner on several previous occasions while fighting fires. On each of these occasions he was admitted to this hospital where, as on the present entry, he recovered rapidly without suffering any serious respiratory complications. Only one other patient in this group, Case 55, lost consciousness for a brief period in the burning building. This patient's husband was close at hand at the time and he pushed her out through the door "just as she swooned." Each of these 3 patients regained consciousness either while they were still in the building or as soon as they reached the outside.

All the 24 patients in this group were conscious on arrival at the hospital and remained so. The bartender was the only one among them who manifested evidence of mild shock on arrival and he recovered rapidly after fluid and plasma therapy was instituted. This patient and 2 others were the only ones in this group who were restless during the first day and required extra sedation for relief.

Only 6 of the 24 patients had any cough. In each instance this was mild and was present for only a few hours. Interestingly enough, the 3 patients who had lost consciousness are all included among these 6 cases. Positive physical signs in the lungs are recorded in only one of these patients. In this case a few scattered musical and crepitant râles were heard during the admission examination but these were no longer heard when the patient was examined again the next morning.

X-rays of the lungs were done in 10 of the patients in this group and these were entirely normal except for minor changes in Case 59 and Case 31. The latter was one of the 3 who had lost consciousness in the building, inhaled quite a bit of smoke and had a slight cough which lasted about a day.

A history concerning previous respiratory infections was obtained in 7 of the 24 cases. None of these 7 had any recent or chronic respiratory illnesses and

<sup>2</sup> At the Massachusetts General Hospital only 3 patients were reported as entirely free of respiratory involvement clinically and by X ray. They had each sustained burns involving 1, 2 and 11 per cent of the body surface, respectively, and the face was included among the burned areas in each instance.<sup>13</sup>

only 2 had had some serious illness in the past,—pneumonia 2 years previously in one and pleurisy 7 years before in the second

Fever, with a rectal temperature of 100°F or higher was present on admission or developed during the first 2 days in 7 of these patients, only one of whom was free of surface burns In 2 patients, Cases 59 and 68, the temperature reached 103° and in 3 others 101° by the end of the first day

Fourteen patients in this group were transferred to other hospitals on their own request or were removed by medical officers of the Army and Navy to nearby military hospitals within the first 18 hours Reports from these hospitals indicated that none of them developed any signs or symptoms of respiratory tract involvement after leaving here The remaining patients stayed for varying periods up to 3½ months depending on the progress of their burns or other injuries The bartender died in the twelfth week and no evidence of recent injury to his respiratory tract was made out at necropsy

*Cases with mild symptoms limited essentially to the upper respiratory passages*

In this group are included the 33 cases classified as Grade 1 in severity The symptoms in these cases were relatively mild and were referable mainly to the upper respiratory tract, although in a few of them there probably was a certain amount of low grade pulmonary involvement Five were entirely free of surface burns, 23 had burns involving 11% or less and the remaining 5 had burns of 20% or more of the body surface The face was involved in every one of the cases in which there were any burns at all and in one of those without any burns of the skin the hair was singed and edema and redness of the pharynx and nasal mucous membrane was noted at the time of admission

Case 38 survived after prolonged and heroic treatment in spite of hemoglobinuria and burns involving 55% of the body surface (3)

Another patient, Case 127, with a 60% burn died after 9 days She too, had hemoglobinuria early, but then developed azotemia and sepsis of the severely necrotic wounds She presented no clinical evidence of severe pulmonary damage or infection until the last 2 days when there were signs of increasing pulmonary congestion Since the condition of the patient was deteriorating, this was considered to be a terminal event Autopsy, however, showed the entire respiratory tract from the larynx down to be involved in a necrotizing, inflammatory process, and there was a hemorrhagic bronchopneumonia similar in character but somewhat less marked than that found in other patients who were considered clinically to have the severest grades of respiratory damage

A history of inhalation of various quantities of smoke and fumes or external physical evidence of such inhalation was obtained in almost every case in this group and 10 of the patients considered that they had inhaled large quantities There was no correlation between the extent and severity of the surface burn and the amount of smoke inhaled as interpreted from the history and physical findings

Eight patients, according to their own story, lost consciousness while still in the burning building However, only one was still unconscious and another was

stuporous on arrival and both became alert again after they had been in the hospital only a few minutes. The other 6 were mentally clear, responded normally when they were first seen in the hospital and, in general, remembered having regained consciousness as soon as they got out of the building or while they were being rescued. One of the latter was a fireman who, in spite of the fact that he was wearing an "all-service mask", apparently "fainted" after inhaling some smoke but came to rapidly as he was being removed by his colleagues. Like the fireman mentioned in the previous group this patient had had similar experiences before and had been treated for them at this hospital, recovering each time without serious respiratory complications.

Four patients among those who had lost consciousness at the fire were also among the ones who remembered previously inhaling rather large amounts of smoke. Two others, however, had considerable amounts of black soot encrusted in their nasal mucous membrane at the time of admission indicating that they, too, had probably inhaled considerable amounts of smoke.

Only one patient in this group, Case 127, was definitely in shock on arrival and remained so off and on during the first 36 hours of treatment in the hospital. This was the only fatal case in the present group. One other patient who had not lost consciousness at any time but had extensive (25%) burns was noted as being cold and nervous and having a rapid thready pulse when first admitted, but her condition improved after she was given fluids and plasma.

The general condition of the patients in this group on arrival and during the first day or two was considered good in 21 cases, fair in 10 and was poor only in the 2 patients with the most extensive burns. The condition of 7 of those rated as fair on admission improved markedly in the first day while the other 3 and the 2 whose condition was rated as poor remained acutely ill for many days. All 7 of the former had burns involving only from 5 to 11 per cent while the latter 5 had burns of 20 per cent or more of the body area.

Restlessness was a feature at the time of admission or shortly thereafter in only 9 cases and was associated with extensive burns in only 1 instance. This restlessness yielded readily to sedation in 2 instances but lasted for 1 to 2 days in 3 cases. In 2 others it was definitely ascribed to pain in the burned areas. Six patients experienced shaking chills or chilly sensations on arrival or within the first few hours. These chills may have been mistaken for restlessness or may have accounted for the latter symptom in some cases since the two are identical in 4 cases. In 1 patient the chills were observed only during or after plasma injections and may have been due to pyrogens contained in the plasma or other parenteral fluids.

symptoms It was the only symptom in 9 cases and was accompanied by hoarseness in 12, by sore throat in 2 and by both hoarseness and sore throat in 4 cases In 1 patient there was wheezing and a sore throat without cough In 4 patients the cough was accompanied by pain or soreness in the chest, usually under the sternum Six patients experienced dyspnea on admission This was mild and lasted only a few hours in each instance In one of these cases the dyspnea was accompanied by slight cyanosis which likewise cleared rapidly

Burns of the mucous membrane of the nose with redness, swelling and moderate amounts of soot were noted on entry in 8 patients In only one instance was this severe and accompanied by epistaxis later when the patient attempted to clear his nose of the crusted exudate The throat was red and looked raw in 6 cases but no severe burns were noted

Abnormal physical signs in the lungs were not elicited throughout the hospital stay in only 8 of the cases in this group In 7 cases the lungs were noted as being clear on the admission examination but a few crepitant râles were heard the next day These râles were not heard on later examination in 4 of these cases while in the others they persisted for several days In 7 additional cases râles (crepitant râles alone in 4 and both crepitant and musical râles in 3) were heard only during the admission examination and not at any later time In the 11 remaining cases râles were heard on admission and for varying periods up to 10 days In 4 cases these were chiefly fine or medium crepitant râles, in 2 they were high and low pitched musical râles and in 4 both types were heard Coarse rhonchi were heard only in 1 of the latter cases The crepitant râles were usually heard only in the base of one or both lungs posteriorly, but the musical râles were heard over all parts of the lungs

There was no cyanosis, and dyspnea of a mild sort occurred only briefly in a few cases No dullness nor abnormal breath sounds suggesting consolidation were noted in these cases Diminished breath sounds, possibly indicating transient partial atelectasis, were made out in the base of the lungs in 3 cases on the third day or later Except in Case 127, this cleared up rapidly

Sixteen of the patients raised various amounts of sputum For the most part this was thick and mucoid in character In 8 instances large amounts of carbon were contained in the sputum for several days and in 5 cases the sputum was blood-streaked after the first day or two In only one case did it become purulent and in Case 127 shreds of fibrin were seen on one occasion

Fever (rectal temperature of 100°F or higher) was present in most of the cases on admission or during the first day or two Only 9 cases were entirely free of fever, 4 of them had no surface burns and the other 5 had burns involving 3 per cent or less of the body surface Temperatures of 100 or 101°F were recorded in 14 cases In 11 of them the fever subsided within 1 or 2 days and in each of these the burns involved 5 per cent or less while in the other 3 cases the burns were more extensive and the fever persisted for longer periods In each of the 10 remaining cases the maximum temperature reached during the first 2 days ranged from 102 to 105° This fever abated by the end of the second day in 4 of these patients in each of whom the surface burns were not extensive In

general, therefore, the early occurrence and persistence of fever in this group was dependent chiefly if not entirely on the extent, and probably on the character of the surface burns

Seven patients had or were convalescent from acute respiratory infections at the time of the fire. These infections included common colds, grippe, laryngitis, bronchitis, and in 1 case, a suppurative streptococcal otitis media. Two other patients had chronic respiratory disease,—bronchitis in one and laryngitis in the other. In none of these cases nor in 4 additional patients in whom there was a previous history of pneumonia or sinusitis did the previous illness seem to have any striking effect on the course of the respiratory injury sustained at the Cocoanut Grove fire.

X-rays of the chest were made on 1 or more occasions in 28 of the cases. The lungs were considered normal in 9 cases, they showed only minor changes (Grade 1) consisting chiefly of slight increases in the hilar shadows and in the bronchial markings in 12 cases and somewhat more definite abnormalities (Grade 2) in 7 instances.

All but 1 of the patients in this group whose skin burns involved less than 5 per cent of the body surface were discharged from the hospital essentially well by the end of the second week. Those with more extensive burns were kept in the hospital for varying periods as indicated by the extent and severity of the burns. One patient, Case 127, died on the ninth day and has already been mentioned in other connections. In no instance were the respiratory symptoms in the present cases sufficient by themselves to keep the patient in the hospital beyond the first few days.

The symptoms and signs in this group of cases were interpreted at the time as representing acute laryngo-tracheo-bronchitis and bronchiolitis, all comparatively mild but nevertheless associated with slight pulmonary congestion. The X ray findings were consistent with this interpretation.

#### *Cases with respiratory symptoms of Grade 3 severity*

There were 19 cases in which the symptoms and signs suggested moderate damage to the respiratory passages with or without mild involvement of the parenchyma of the lung. All had some surface burns, but these were not extensive in most of them. In 13 cases they involved 6 per cent or less, in 1 each they were of 10, 13 and 28 per cent, respectively and in the remaining 3 they involved 30 per cent or more of the body surface. The last 3 patients died and the others recovered.

The face was included in the burned area in every instance except in one patient in whom only the right hand was burned. This patient and the two already mentioned among those essentially free of respiratory damage were the only ones admitted to this hospital with burns of any part of the body surface in whom the face was spared. In 8 cases there were mild burns of the nose as evidenced by anged vibrissae, edema of the mucous membranes which were caked with soot. In some instances there was epistaxis or occlusion of the nares with crusted red exudate. The tonsillar pillars and soft palate were red and slightly swollen in 2 cases.

symptoms It was the only symptom in 9 cases and was accompanied by hoarseness in 12, by sore throat in 2 and by both hoarseness and sore throat in 4 cases In 1 patient there was wheezing and a sore throat without cough In 4 patients the cough was accompanied by pain or soreness in the chest, usually under the sternum Six patients experienced dyspnea on admission This was mild and lasted only a few hours in each instance In one of these cases the dyspnea was accompanied by slight cyanosis which likewise cleared rapidly

Burns of the mucous membrane of the nose with redness, swelling and moderate amounts of soot were noted on entry in 8 patients In only one instance was this severe and accompanied by epistaxis later when the patient attempted to clear his nose of the crusted exudate The throat was red and looked raw in 6 cases but no severe burns were noted

Abnormal physical signs in the lungs were not elicited throughout the hospital stay in only 8 of the cases in this group In 7 cases the lungs were noted as being clear on the admission examination but a few crepitant râles were heard the next day These râles were not heard on later examination in 4 of these cases while in the others they persisted for several days In 7 additional cases râles (crepitant râles alone in 4 and both crepitant and musical râles in 3) were heard only during the admission examination and not at any later time In the 11 remaining cases râles were heard on admission and for varying periods up to 10 days In 4 cases these were chiefly fine or medium crepitant râles, in 2 they were high and low pitched musical râles and in 4 both types were heard Coarse rhonchi were heard only in 1 of the latter cases The crepitant râles were usually heard only in the base of one or both lungs posteriorly, but the musical râles were heard over all parts of the lungs

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Fever (rectal temperature of 100°F or higher) was present in most of the cases on admission or during the first day or two Only 9 cases were entirely free of fever, 4 of them had no surface burns and the other 5 had burns involving 3 per cent or less of the body surface Temperatures of 100 or 101°F were recorded in 14 cases In 11 of them the fever subsided within 1 or 2 days and in each of these the burns involved 5 per cent or less while in the other 3 cases the burns were more extensive and the fever persisted for longer periods In each of the 10 remaining cases the maximum temperature reached during the first 2 days ranged from 102 to 105° This fever abated by the end of the second day in 4 of these patients in each of whom the surface burns were not extensive In



general, therefore, the early occurrence and persistence of fever in this group was dependent chiefly if not entirely on the extent, and probably on the character of the surface burns

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X-rays of the chest were made on 1 or more occasions in 28 of the cases. The lungs were considered normal in 9 cases, they showed only minor changes (Grade 1) consisting chiefly of slight increases in the hilar shadows and in the bronchial markings in 12 cases and somewhat more definite abnormalities (Grade 2) in 7 instances.

All but 1 of the patients in this group whose skin burns involved less than 5 per cent of the body surface were discharged from the hospital essentially well by the end of the second week. Those with more extensive burns were kept in the hospital for varying periods as indicated by the extent and severity of the burns. One patient, Case 127, died on the ninth day and has already been mentioned in other connections. In no instance were the respiratory symptoms in the present cases sufficient by themselves to keep the patient in the hospital beyond the first few days.

The symptoms and signs in this group of cases were interpreted at the time as representing acute laryngo-tracheo-bronchitis and bronchiolitis, all comparatively mild but nevertheless associated with slight pulmonary congestion. The X ray findings were consistent with this interpretation.

#### *Cases with respiratory symptoms of Grade 2 severity*

There were 19 cases in which the symptoms and signs suggested moderate damage to the respiratory passages with or without mild involvement of the parenchyma of the lung. All had some surface burns, but these were not extensive in most of them. In 13 cases they involved 6 per cent or less, in 1 each they were of 10, 13 and 28 per cent, respectively and in the remaining 3 they involved 30 per cent or more of the body surface. The last 3 patients died and the others recovered.

The face was included in the burned area in every instance except in one patient in whom only the right hand was burned. This patient and the two already mentioned among those essentially free of respiratory damage were the only ones admitted to this hospital with burns of any part of the body surface in whom the face was spared. In 8 cases there were mild burns of the nose as evidenced by singed vibrissae, edema of the mucous membranes which were caked with soot. In some instances there was epistaxis or occlusion of the nares with crusted red exudate. The tonsillar pillars and soft palate were red and slightly swollen in 2 cases.

All of the patients in this group either remembered inhaling some smoke and fumes or gave physical evidence of having done so when they first arrived in the hospital. In 13 of the cases there was reason to believe that the patient had inhaled at least moderate if not large amounts.

Eight of the patients lost consciousness while still in the building and all but one of them probably inhaled fairly large amounts of smoke. Four of these patients remembered having attempted to escape and succeeded in reaching one of the exits before they lost consciousness. These four regained consciousness soon after they got out of the building and a fifth was revived as she was being dragged out by another patron. By the time that these 8 patients were admitted to the hospital only one, Case 117, was still unconscious and another, Case 110, was quite disoriented while the rest were all conscious and rational.

Cases 110 and 117 and one of the others who had lost consciousness briefly manifested evidences of shock either on arriving at the hospital or very shortly thereafter. Two of these 3 patients responded readily to plasma and fluid therapy and all the signs of shock cleared within a few hours, the third, Case 117, remained in shock until he died less than 4 hours after reaching the hospital. His were the most extensive burns of this group of cases and involved an estimated 40 per cent of his body surface. The general condition of the patients in this group on arrival and for the first few hours was considered to be good in 4 cases, fair in 13 and poor only in 2 of the cases that ended fatally.

Restlessness was an early feature in 10 cases, including Case 110, one other patient who was in mild shock on arrival and 2 additional patients who had a brief period of unconsciousness at the fire. In Case 110 delirium and periods of disorientation recurred off and on for several days. The surface burns were extensive in only 3 of these 10 cases, nevertheless much of the restlessness apparently resulted from pain and discomfort in the burned areas and persisted for periods of 1 to 5 days. In four of the patients, including Case 110, however, it is possible that tremors or mild convulsive attacks may have been interpreted as chills. Vomiting occurred on admission in 9 patients and persisted for several hours in some and up to 2 days in others. The vomitus at first contained a good deal of black carbonaceous material mixed with mucus.

The most frequent symptoms referable directly to the respiratory tract were cough and hoarseness which were both present in 16 of the cases. One or the other of these 2 symptoms was present alone in the remaining 3 cases. Moderately severe sore throat accompanied the cough and hoarseness in 5 of the cases. Pain in the chest on coughing was noted in only 1 instance. The cough was mild in most of the patients and often was paroxysmal with long free intervals. The hoarseness, on the other hand, was more marked and was considered severe in 10 cases. The cough usually persisted for only 2 to 5 days and up to 8 days in 1 case, while most of the patients continued to be hoarse for from 1 to 2 weeks. Only 1 of the patients is recorded as having moderately severe dysphagia. Dyspnea, usually mild and of short duration, was experienced by 10 of the patients in this group. In 2 cases it lasted for the first 2 days only but was accompanied by intermittent periods of somewhat labored respirations during

the first 18 hours In 3 patients slight dyspnea first appeared on the third or fourth day and one of them also had brief spells of slightly labored respiration after that time Cyanosis accompanied the dyspnea in only 1 case and was brief and mild in that case Except for the hoarseness and cough, the respiratory symptoms improved rapidly in most of the cases

In the lungs the signs were similar to those found in the cases of the preceding group but they were found more frequently and persisted longer Only in 1 case of this group, Number 109, were no abnormal physical signs made out In 7 cases in which the lungs were examined at the time of entry and noted as being clear at that time râles appeared on the following day In 3 of these 7 cases, sonorous and sibilant râles appeared first and on later examinations fine and medium crepitant râles were made out at the base of one or both lungs posteriorly In the other 4 only crepitant râles were heard but only the musical râles were noted in the admission examination of 3 of these cases In 3 of the remaining 4 cases only a few crepitant râles were heard at any time In the last case, the patient who died shortly after entry (Case 117), only inspiratory wheezes were heard throughout both lung fields, but no evidence of obstruction or any signs suggestive of pulmonary edema were made out up to the time of death The râles in the present group were heard for only 1 to 5 days in 4 cases but in the rest these signs persisted for 7 to 12 days

Signs of consolidation were not made out in any of these cases at any time In 4 cases, however, diminished breath sounds were made out on one or more occasions in the dependent portions of the back on one or both sides This usually occurred only after the first few days and suggested partial atelectasis of these parts of the lungs

Small amounts of mucoid sputum were raised by 11 of the patients In most cases this contained much soot especially on the first day, and in 3 instances there were small amounts of blood later In 3 other patients the sputum became purulent

Some changes in the X-ray were noted in all but one of the 16 cases in whom roentgenograms were done In 7 of them the changes were minor and involved chiefly the hilar shadows and bronchial markings, in 7 others minor changes in the lung were also noted, but only 1, Case 110, had moderately extensive changes and these cleared rapidly

Fever was present on admission or developed within the first 2 days in 16 of the cases in this group The maximum temperature reached a level above 103°F in 1 case, 102° in 9 cases, 101° in 3 cases and 100° or slightly higher in the remaining 3 cases This fever abated within 1 or 2 days in all but 3 of these cases and in them it persisted for several additional days In these 3 cases the burns involved 10, 28 and 30 per cent of the body surface, respectively

A history of recent or chronic upper respiratory tract infection was obtained from 5 patients in this group In 3 of them the symptoms were those of a common cold and in the other 2 there was recurrent laryngitis Neither the febrile course, the symptoms, nor the physical signs in these cases differed materially from those of the other patients in this group

Three patients of the present group were transferred to other hospitals within 36 hours. The hospital stay of the other recovered cases, exclusive of return admissions for plastic operations, varied from 11 to 155 days and averaged 45 days. In general, the longest periods of hospitalization were in the patients with the most extensive surface burns and the shortest in those with only minor burns (see table 5).

The 3 patients in this group who had burns of 30 per cent or more of their body all died,—the first in 4 hours, the second on the twenty-eighth day and the third early in the sixth month. No autopsy was done in the first case, No 117, but the death was probably related to the shock which failed to respond to therapy. There was no clinical evidence of respiratory embarrassment or of pulmonary edema in this case. In Case 110, the death occurred at another hospital 6 days after the patient was taken there for skin grafting. Although this patient had moderate symptoms and X-ray changes in the lungs during the first few days, he was free of respiratory symptoms and his lungs were clear to physical and X-ray examination at the time of transfer and for several days previously. Soon after arriving at the other hospital he developed an acute febrile episode associated with some respiratory distress. Autopsy in this case revealed an extensive and diffuse necrotizing process involving the trachea, bronchi and lungs with numerous small staphylococcus abscesses in the lung tissue. In the third case, No 109, the lungs were essentially normal at necropsy and death resulted from inanition plus infection of the granulating surfaces.

The signs and symptoms in this group of cases were interpreted as evidence of laryngo-tracheo-bronchitis with congestion and occasionally, with transient partial atelectasis of the lungs in the dependent portions. The X-ray findings were consistent with this interpretation.

#### *Cases with respiratory symptoms of Grade 3 severity*

There were 25 cases with symptoms of severe respiratory damage but without evidence of marked and prolonged obstruction or of extensive pneumoma. Only 1 of them, Case 47, was free of surface burns but her nasal and pharyngeal mucous membranes were red and swollen and the laryngoscopist found that her vocal cords were signed. In the majority, the burns were rather limited in extent—they involved 7% or less in 15 cases, from 14 to 25% in 3 and from 30 to 65% of the body surface in the remaining 7 which were the only fatal cases in this group. The face was included among the burned areas in every instance.

Most of those from whom adequate histories were obtained recalled having inhaled much of the irritating smoke and fumes and the others probably also had quite a dose of it judging from the findings they presented on arrival. Indeed there was a strong odor of smoke on the breath of some of these patients which persisted and permeated the air of some of the wards for several days.

Unlike the previous groups in which loss of consciousness was the exception, all but 3 of the patients in the present group lost consciousness in the burning building after inhaling some of the smoke and fumes. Some details of what

happened at the fire were given only by Case 16. She apparently had a prolonged exposure within the building before she was helped out by a fireman and was somewhat confused for more than a day in the hospital. Others could recall having taken only 2 or 3 breaths of the black, heavy and irritating smoke and remembered nothing thereafter until they found themselves either outside of the building, on their way to the hospital or on the admission floor. Only 6 of those who lost consciousness at the fire, including 4 who later died, were unconscious, stuporous or disoriented at the time when they arrived in the hospital or for brief periods thereafter. One additional fatal case lost consciousness soon after entry. Most of the others had regained consciousness either as soon as they reached the outdoors or while on their way to the hospital.

The general condition of the patients during the first few hours was considered to be poor in 11 cases, including 6 of the fatal cases, the patient without burns of the skin and the one who recovered and had the most extensive surface burns. In 11 others including the remaining fatal one, the condition at that time was fair, and in the remaining 3 it was good. Evidences of shock were found on admission in all of the fatal cases and in 3 who recovered. The latter all had lost consciousness at the fire but the burns were extensive (25%) in only one of them. In the other 2, only 4 and 6%, respectively, of the total skin areas was burned.

All the patients in this group except 3 who recovered were restless on arrival or became so during the following morning or afternoon. In a few, the restlessness was related to pain from the burns, but in others it was associated with spells of choking and labored respirations and presumably was a manifestation of anoxia. In still others it may have been of cerebral origin since it occurred in patients who were unconscious or disoriented during the first few hours in the hospital and was associated with muscular twitchings in 1 and with a convulsive seizure in another. The restlessness in most cases was not marked and lasted only a few hours, but in some it persisted up to 2 or 3 days.

Six of the patients had shaking chills during the first few hours after their arrival in the hospital. Most of these chills occurred during or shortly after intravenous injections of plasma or other fluids and probably resulted from injected pyrogens. Vomiting occurred in 14 of the cases, mostly at the time of admission, but in a few it continued for several hours and in one for several days. The vomitus in many of the cases contained soot and other dark brown material including some changed blood.

Hoarseness and cough were present in every one of the patients except those who were essentially comatose. Sore throat accompanied the hoarseness and cough in 11 of the patients and most of the latter also had dysphagia. One had a choking spell each time he attempted to swallow—even fluids. These symptoms were usually manifested at the time of admission but increased rapidly in severity during the first few hours. The cough usually subsided in from 3 days to a week. The hoarseness persisted throughout the period of hospitalization in those who left before the end of the third week and for about 4 weeks in a few of the others.

All but 2 of the patients were dyspneic on admission or became so in the first few hours. The dyspnea increased in severity during the first day but either

subsided entirely or improved considerably during the next 2 or 3 days. A number of the patients also had slight to moderate cyanosis. A few had episodes during the first two days when they gasped for breath. In 11 patients there was definite wheezing or asthmatic type of breathing associated with the labored respirations and persisting for 3 to 10 days.

Definite stridor and labored respirations necessitating the use of accessory muscles were noted in 15 cases including 6 of those who had the wheezing or asthmatic type of breathing and also 3 of the fatal cases. The stridor was noted on admission in some cases, but it usually first became manifest some time later, even up to the third day. It was recurrent in most instances but was persistent in others and lasted from a few hours up to 2 days. In the 3 fatal cases it persisted to the time of death. Some of the patients had periods when they felt as though they were being choked and they had to sit upright in order to breathe. One of those with the most severe stridor and choking spells (Case 53) was almost immediately and completely relieved during the second day after he coughed up a large tracheal cast consisting of a dense fibrinous pseudomembrane about 9 cm. long, 2 cm. wide and about 1 mm. thick. Others were partially or temporarily relieved after raising smaller shreds of fibrinous or thick mucoid material or after similar material was removed by suction.

During the first day or two the sputum was scant, thick and mucoid. It contained varying amounts of soot and had an odor of smoke. In some instances it later became mucopurulent, more copious and less viscid. In 13 of the cases it was streaked with fresh blood or contained changed blood constantly or intermittently for several days. Smears of the sputum in most instances showed ciliated columnar cells and sheets of large squamous epithelial cells presumably from the tracheal and pharyngeal mucosa. In a few cases shreds of fibrin or pieces of thin membranous material were seen either in the sputum or in the bloody mucoid material obtained by tracheal or pharyngeal suction.

The nose was affected both externally and internally in 14 of the cases. Externally the nose appeared red, swollen and sometimes blistered. The vibrissae were singed in a few of the cases. The mucous membrane was usually red and swollen. The nares were occluded for several days both as a result of the swelling and by the presence of crusts of black mucus, serum and blood. There were considerable amounts of carbon particles embedded in the mucous membrane and mixed with the secretions. Bleeding in small amounts occasionally resulted from attempts to clear the nose of this material.

In about half of the cases the throat appeared red, raw, dry and sometimes edematous. Singed areas and small blisters were often noted on the soft palate. Some of the blood streaks and the sheets of epithelial cells seen in the sputum probably originated from these areas. Laryngoscopy was done in several of the cases with marked laryngitis and stridor but, under the stress at the time, the findings were not recorded in every instance. In Case 47 the vocal cords were noted as being singed and in Case 69 edema of the glottis was seen.

The signs in the lungs were similar to those in the preceding group but they were more extensive and, in addition, evidence of consolidation was found in a

few cases. Among those who recovered, the lungs were noted as being clear on admission in only 3 cases and in 3 others only a few squeaks were heard at that time. Within the next few hours, however, musical râles usually bilateral, diffuse, and sibilant or sonorous in character were heard in almost every case. After the first 2 or 3 days, there were very high pitched râles associated with poor respiratory murmurs similar to the sounds heard in some asthmatic subjects or in patients with bronchiolitis. Fine or medium crepitant râles were heard at the base of one or both lungs posteriorly in all cases. Loud rhonchi or showers of crepitant râles in the upper or anterior parts of the lungs were heard only in an occasional case. In those who recovered these signs persisted from from 6 to 24 days and were still present at the time of discharge in some of those who left the hospital before the end of the third week.

Signs of consolidation appeared between the third and eighth day in 6 of the recovered cases. They were limited to parts of one lower lobe in 5 cases, and of both lower lobes in the sixth. In Case 22, an extensive area of consolidation proved later to be a dense and completely atelectatic left lower lobe which in oblique and lateral X-rays was seen as a triangular area of density behind the heart shadow. It was, therefore, not readily made out in the antero-posterior views in the early films.

The breath sounds were diminished in 13 of the recovered cases. This was first noted between the third and twelfth day in the dependent portions of one or both lungs in patients who had been permitted to lie quietly without changing position for long intervals. It was often accompanied by slight dullness and was usually transient and migratory. Changes in position or paroxysms of coughing often produced changes in the signs so that the breath sounds were more normal. These signs suggested partial atelectatic collapse of areas in the lung. Only in Case 22 were the signs those of complete atelectatic collapse of an entire lobe and they were more suggestive of consolidation, as already mentioned. That lobe apparently remained completely collapsed throughout the entire month that the patient remained in this hospital and for some time thereafter while he was receiving further treatment for his burns at a Naval hospital.

In 3 of the 4 cases in which death occurred early, coarse bubbling râles, loud rhonchi and gurgling sounds, probably resulting from accumulation of moisture in the upper air passages, were heard from the time of admission to the time of death. In the fourth case, wheezing and stridor predominated throughout the 10 hours which the patient lived, but no moist or bubbling râles were heard. In the 2 patients who died after several days (Cases 113 and 131) crepitant râles were heard in both bases and sonorous râles were heard throughout the lungs. In one of these cases signs of consolidation were made out on the day before death.

Autopsies were done only in the last 2 cases. Both revealed extensive necrotizing and pseudomembranous laryngo-tracheal bronchitis and bronchiolitis with areas of dense atelectatic collapse, and some small areas of hemorrhagic bronchopneumonia. In Case 131, there had been hemoglobinuria early and azotemia later, and large kidneys with arterial thrombi were found at necropsy. Death

in the other 5 cases was attributed primarily to shock. In one case with a 60% burn the possibility that pulmonary edema was an important contributing factor or even the chief immediate cause of death could not be excluded. Hemoglobinuria was noted in 3 of these 5 cases. In 2 of them, this finding was verified by the studies of Shen, Ham and Fleming (10) but in the third and in one of the recovered cases in this group, the occurrence of hemoglobinuria was based on the clinical appearance of the voided urine and was not verified by laboratory tests.

X-rays of the chest were made in 20 cases of this group. None were found to be entirely normal throughout and in only 2 of the cases were the abnormal findings limited to increases in hilar shadows and bronchial markings. In the others there were areas of atelectasis and of mottled densities involving various amounts of the lung. On the whole, the X-ray changes were consistent with the character and extent of the clinical findings.

A history of recent respiratory infections was obtained in 6 of the cases in this group. One was recovering from a "head cold" and another from a "chest cold" at the time of the fire. Three others had recurrent or chronic upper respiratory tract infections and one had chronic bronchitis. The latter, Case 53, was the one who coughed up the membranous cast and obtained immediate relief thereby. The patient with the singed vocal cords had a history of recurrent asthma but had no definite manifestations of this condition during the present hospital entry. Three other patients had had pneumonia or pleurisy on one or more occasions in the past. In no instance did the respiratory symptoms or even the febrile course seem to be affected in any way by the previous illness.

Two patients had a previous history of rheumatic fever and physical signs of mitral stenosis. When these patients were noted as having dyspnea and râles in the lungs at the time of entry, they were digitalized and maintained on digitalis for a few days. The symptoms and pulmonary signs in these cases also did not seem to be aggravated by the heart lesion.

As in the preceding group, fever was a feature of the early course in the hospital in all of the present cases, but although higher maximum temperatures were attained, the fever was no more prolonged. All but 5 of the cases had some fever on the day of admission. In 2 of these 5 cases there was a brief rise in temperature in the fifth day only, to 101°F in one case and to 105° in the other, while in the remaining 3 the temperature rose to 101° or 102° on the day after admission and stayed at about the same level for 2 or 3 days. The maximum temperature attained in the remaining cases was 101° or slightly higher in 3, 102° in 8, 103° in 2 and 104° or higher in 5 cases. The fever usually subsided in from 1 to 4 days but in a few some low-grade fever persisted for several days. In one patient who died 29 hours after the fire (Case 115, one of those with hemoglobinuria) the temperature rose steadily during the last few hours to reach a maximum of 109° and in Case 113 there was irregular fever, occasionally reaching 103°, until the ninth day when the temperature rose steadily to 107° and the patient died.

The period of hospitalization in the recovered cases of this group, as in the previous one was related primarily to the extent and severity of the surface



burn and, except perhaps in individual cases, was not influenced by the severity of the respiratory complications. Thus the average hospital stay of the recovered cases was 36 days in the present cases and 41 and 45 days, respectively in those with Grade 1 and 2 severity. In the patients who died, on the other hand, the severity of the respiratory complication probably hastened the fatal outcome.

The signs and symptoms in this group of cases were interpreted as representing chiefly laryngo-tracheobronchitis and bronchiolitis with congestion and atelectasis of the dependent portions of the lungs and some bronchopneumonia in those who died after the first few days. There was no evidence of severe obstruction to the air passages and the deaths were attributed chiefly to extensive burns and associated shock.

*Cases with evidence of obstruction to the respiratory passages or with extensive pulmonary involvement*

The final group of 30 cases includes the ones with the severest respiratory symptoms classified as Grade 4. Most of these patients soon after they arrived developed marked obstruction to their air passages and tracheotomies were done in 18 of them in an attempt to relieve the obstruction. The other 12 all died with what was considered to be progressive respiratory embarrassment though not necessarily as a result of obstruction. The events which transpired on admission and during the early part of the hospital course in most of these cases happened so rapidly that it was not possible to make or record any extensive or detailed observations. A slight conception of the urgency of the problems confronting the staff may be gained from the fact that 14 of the 18 tracheotomies were done during the first 24 hours and only 3 of the 12 who did not have tracheotomies done lived more than 43 hours after the fire. Scattered details of the early course and of the findings at the time of admission are available from which the clinical picture could be pieced together. These are from notes made at the time by nurses and by members of the hospital staff, but mainly by Dr. George H. A. Clowes, Jr. who was then Dr. Lund's resident assistant for the study of burns.

Three patients in this group were free of surface burns but only one of them survived. The burns were extensive in 11 cases, involving 30 to 65% of the body surface in 8, and 20 to 25% in the other 3, they were moderate in extent in 13 cases, including 5 with burns of 10 to 15% and 8 with 5 to 8% involvement. The 3 remaining cases had minor burns involving up to 4% of the surface area. Here again the face and nose were involved in every case.

Almost every one in this group presented objective evidence of having inhaled large amounts of smoke the odor of which could be made out on their breath at a considerable distance and persisted for many hours. From what was learned from those patients who were capable of giving a history it may be presumed that they all had lost consciousness while they were still within the burning building. By the time they were first seen in the hospital and during the first few hours thereafter, only 10 still remained conscious and rational. The rest were either completely comatose, stuporous or irrational and disoriented. Six patients who were conscious on arrival rapidly became stuporous or comatose.

The general condition of all these patients was considered to be poor at the time of admission or degenerated rapidly after their arrival. Indeed, 5 of them were essentially moribund when first seen and died within 7 hours. Only 4 of the 30 were considered to be in fair condition when first admitted—one of them died on the third day, a second died on the fourth day and the other 2 survived. Manifestations of shock were noted in 15 cases but in 2 of them it did not develop until a few hours after entry. In 9 of those who had a tracheotomy, including the 3 who recovered, and in 2 of those without tracheotomy there are sufficient data to indicate that shock was not present on admission and did not develop. In some of them the systolic blood pressure was often elevated due to the struggling and excitement. Restlessness, however, was a feature of all of the cases and was quite marked. In a few it was intermittent and some patients became irrational at times. The restlessness and excitement were chiefly the result of anoxia, although pain from the surface burns may have been a contributing factor in some instances and a few patients felt very dry and thirsty. The restlessness was not readily relieved by sedation. Chills were observed at the time of admission in 2 cases and after an injection of plasma in a third.

Vomiting occurred in the hospital in 19 cases and was severe in 5 of them. In 3 it occurred only at the time of admission, while in some of the others it persisted for several hours. The early vomitus contained much carbonaceous material and mucus.

Hoarseness was present in practically every patient and increased rapidly in severity in those who lived for more than a few hours. It was accompanied by cough in all but 3 patients, each of whom was practically moribund from the time of entry. The cough was severe in the 3 patients who survived, but the others were all too sick to cough very vigorously or frequently.

Only 6 patients complained of sore throat. Many of the others probably failed to do so only because of their extremely poor condition, since their throats were red, dry and raw in appearance at the time of admission. There were 8 cases with burns of the lips and nose. The nasal mucous membrane in these cases was swollen and black with soot and the nasal hairs were burned.

Difficulty with breathing was the outstanding feature of all the cases in this group. Dyspnea of some degree with rapid, shallow respirations was noted at the time of admission and was accompanied by some stridor except in 2 patients with very extensive burns. The lungs in one of them, Case 126, were noted as clear, and in the other, Case 120, only a few râles were heard at the bases in the admission examination but both were breathing comfortably at that time and for the next 24 hours. After that, they both developed intermittent spells of dyspnea and labored breathing which increased in severity. Râles appeared in the lungs and increased until they died, one 18 hours and the other 54 hours later.

In 5 cases the dyspnea and stridor were present in a moderately severe form from the time of admission. In all of the cases, however, the dyspnea increased either progressively or spasmodically until the patient died or until relief was obtained from tracheotomy. Audible wheezes accompanied the labored breathing in 16 cases and was usually present from the time of admission. Only 2 of

the patients complained of pain or of a sense of constriction in the chest. Definite cyanosis was noted in 12 cases, chiefly during spells of respiratory obstruction.

Numerous râles were heard in every case. In only 2 instances were the lungs noted as clear at the time of admission and in them râles were heard on the following morning. There were only 2 cases in which the lungs cleared either partially or completely for brief periods after râles were once heard. In most of the others these signs increased progressively. In general, the râles in the present cases were more numerous, louder and coarser than in the previous groups. In 10 cases the breathing was noisy, and gurgling tracheal sounds suggesting the presence of secretions in the pharynx were heard from the time of admission or shortly thereafter. In the remaining cases rather low-pitched musical râles or rhonchi predominated throughout the lungs and medium, coarse and sometimes bubbling râles were heard mostly at the bases posteriorly. In some instances these râles were also heard in the upper and anterior parts of the lungs. In all the fatal cases the râles persisted to the time of death. In the 3 patients who recovered, rhonchi or wheezes were heard throughout the lungs and crepitant râles were heard only at the bases. In one of the latter, these signs persisted for only 9 days and in the other 2 they were heard for 2 weeks. After that time the lungs were clear in all 3 of these cases.

Definite signs of consolidation were made out only in Case 107, and were first recognized shortly before death which occurred on the seventh day. Some dullness and diminished breath sounds suggesting partial or localized areas of atelectasis were elicited within the first few hours in 2 fatal cases and death occurred within the first 2 days in both instances. The same signs were noted on the eighth day or later in 2 other patients who recovered and in them they were transient.

The character of the sputum was noted and recorded in 18 cases of this group. In view of the interpretation of the events which generally prevailed at the time, namely, that the patients were suffering from pulmonary edema, it is significant that the sputum in every instance was described as scant, thick, viscid and mucoid. Only in a single case was it noted as being thin, frothy or copious during the first day or so. Similar viscid material was obtained with difficulty by suction in the cases in which this procedure was employed. The sputum as well as the material obtained by suction was black with soot during the first day or so. Later on, the sputum in some instances became more profuse and blood streaked or contained frank blood,—even in some patients in whom tracheotomies had not been done. The blood may have originated from the upper respiratory passages in some cases. The bloody sputum looked like that frequently seen in patients with pulmonary infarcts and indeed, areas of infarction were noted at autopsy in the lungs of some of these cases. Diffuse blood-tinged sputum suggesting pulmonary congestion or edema, and rusty sputum of the type seen in lobar pneumonia were seen.

These findings in the sputum are of particular interest in the interpretation of the causes of the pulmonary lesions. It cannot be argued that the scant and viscid character of this sputum and the absence of the characteristics ordinarily

seen in the secretions of patients with pulmonary edema were due to dehydration or to the use of plasma in the present cases. To be sure, the average amount of plasma which these patients received was 8.5 units of 2,125 cc and only 8 of them received less than one liter. Other fluids, however, were freely used in most of these cases in addition to the plasma. After excluding 6 patients who died in the first 9 hours without the benefit of a large fluid intake, the average intake per patient was 3.3 liters in addition to the amount of plasma administered. Almost all of this added fluid was given intravenously and the average amount given in the form of physiological solution of sodium chloride was 1.7 liters. Some may have received additional amounts by mouth that were not recorded. The effects of these fluids on the pulmonary lesions are discussed in more detail elsewhere (15).

Roentgenograms were not taken during the first 36 hours so that this type of corroboration of the early physical findings was not available in the patients who died before that time. X-rays of the chest were taken on the second day or later in 12 cases. These showed extensive pulmonary infiltration as well as marked increases in the hilar and bronchial shadows in all but 2 cases in which only minor areas of density were visualized in the lungs. In some instances bronchi were seen to be thickened and dilated all the way to the diaphragmatic surface. The areas of density were small and nodular but there were no extensive confluent areas or areas suggesting consolidation.

No temperature records are available in the 6 patients who died in the first 9 hours. Some fever (100.2°F or higher) was present in all but 2 of the remaining cases. The maximum temperature rose to 105° in 4 cases. Terminal hyperpyrexia with temperatures reaching 106° to 107.5° were noted in 4 other patients. In most instances the elevated temperatures were recorded during the first few hours but in a few the fever was first noted on the following day or even later. The pulse rate usually corresponded to the height of the fever except in 2 cases in which the pulse was disproportionately rapid. One of them, Case 119, developed auricular fibrillation on the third day. This patient had definite symptoms of obstruction and was found by the laryngologist to have edema of the glottis and larynx.

A history of antecedent respiratory diseases was obtained in only 4 cases of this group. Two patients who died, were just getting over an attack of the common cold and one who recovered had a sore throat at the time of the fire. In these cases the acute respiratory infection probably had very little effect on the clinical course. In another recovered case, No. 90, there was a history of asthma which may have aggravated the early obstructive symptoms sufficiently so that a tracheotomy was deemed necessary. Following the tracheotomy this patient manifested very little respiratory embarrassment and her condition improved so rapidly that the tracheotomy tube was removed after only 2 days. She had very few symptoms of respiratory obstruction after that time.

Dark colored urine, probably resulting from hemoglobinuria, was seen in 6 of the present cases, but this was proved in only 3 of them (10). The burns in these 3 and in 2 others involved from 30 to 65% of the body surface, but in the

sixth case, they were of only 5% All these 6 patients died, one during the first day, 2 during the second and the other 3 from the third to the sixth day

*Cases in which tracheotomy was performed*

The deaths in the present group were due to 2 different types of respiratory failure In the majority, death resulted from complete obstruction to the airways, and usually after previous similar episodes In some the obstructive phenomena were temporarily relieved by tracheotomy while in others this operation either was done too late or failed to give relief A few in whom the tracheotomy seemed to give considerable relief continued to have spells of sudden and complete obstruction Some of the latter were found dead before any active measures could be taken while others were again temporarily relieved by suction through the tracheotomy tube or through a bronchoscope inserted through the tracheotomy wound

A summary of some of the salient features of the tracheotomy cases is given in table 3 The intervals after the fire when the operation was done and the results are as follows

Less than 12 hours—6 cases	0 survived
13-24 hours—8 cases	3 survived
More than 24 hours—4 cases	0 survived

The tracheotomies were done for the relief of symptoms of obstruction which were persistent and usually progressive, with periods of exacerbation In 3 patients they were done during an episode of complete obstruction after periods when the patients were comparatively comfortable In none of these 3 cases was the tracheotomy successful although in one instance life was maintained by artificial respiration for an hour after the operation Five other patients lived a few minutes or up to an hour after the tracheotomy In some the operation was technically difficult due, in part, to the marked edema of the neck resulting from the burns and there was considerable hemorrhage at the time of operation in a few

Most of those who survived tracheotomy for more than a few hours had varying amounts of subcutaneous emphysema extending into the neck and subclavicular regions and, in some instances, over the pectoral and axillary regions This emphysema could be made out clinically in some while in others it was seen only in the X rays Case 91, one of the patients who recovered and had repeated bronchoscopic suction through the tracheotomy wound, had a rather large hemorrhage on the sixteenth day, 4 days after the tube was removed

Another patient, Case 98, apparently obtained marked relief from the tracheotomy which was done 10 hours after entry She was soon able to breathe through her mouth with the tracheal tube blocked The tube was, therefore, removed after 2 days, but 8 hours later she had another sudden attack of dyspnea, rapidly developed complete obstruction which could not be relieved by bronchoscopic suction and the patient died before the tube was replaced

The tracheotomy tubes were removed in the 3 survivors 2, 11 and 15 days, respectively, after the operation. In each instance the external orifice of the tube was corked periodically and the patient was allowed to breathe with the tube in place for increasing periods before it was finally removed. These 3 patients were discharged from the hospital on the sixty-sixth, twentieth and twenty-third day respectively. The second of these patients was still coughing and raising a good deal of sputum at the time but he made an uneventful trip across the

TABLE 3  
*Cases with tracheotomy, indications and results*

CASE NO	PER CENT OF BODY SURFACE BURNED	TRACHEOTOMY					REMARKS
		Hours after entry	Acute obstruction*	Immediate relief	Time elapsed		
					To death	Tube removed	
					hours	days	
90	5	20		+	Lived	2	
91	6	16		+	Lived	11	Frequent bronchoscopic suction through wound Hemorrhage 4 days after tube was removed
92	0	14		+	Lived	15	Tube corked for a few hours daily after sixth day
93	5	2		+	29		Never regained consciousness
94	25	34	+	0	$\frac{1}{2}$		Operation rapid and uneventful Artificial respiration without effect
95	60	20		+	7		Artificial respiration for few minutes
96	6	9		0	$\frac{3}{4}$		
97	4	15		0	$\frac{1}{2}$		
98	1	10		+	68	2 $\frac{1}{2}$	Much bleeding at operation Sudden obstruction 8 hours after tube was removed
99	20	6		0	$\frac{1}{2}$		
100	13	23		0	$\frac{1}{2}$		
101	14	11		+	23		Convulsive twitchings last 3 hours
102	65	27		+?	3		Hemorrhage from wound 1 $\frac{1}{2}$ hours after operation
103	4	10		+	5 $\frac{1}{2}$		Hemorrhage 5 hours postoperative, easily controlled but dyspnea and cyanosis increased
104	7	83	+	0	0		Operation difficult
105	15	17		0	$\frac{1}{2}$		Artificial respiration without effect
106	35	49	+	0	1		Artificial respiration without effect
107	12	18		+	142		Intermittent relief from oxygen under positive pressure

\* All had progressive symptoms of obstruction

continent on the day he was discharged and he continued his convalescence under the care of his physicians after reaching the West Coast

#### *Deaths in cases not subjected to tracheotomy*

In addition to the 15 deaths in patients subjected to tracheotomy, there were 4 in whom death was due to progressive obstruction with an acute exacerbation

These patients died after 25 (Case 123), 38 (Case 122), 79 (Case 120) and 120 (Case 119) hours, respectively. Autopsies were done in 2 of them and in each instance showed the same type of edematous and pseudomembranous inflammation of the larynx, trachea and bronchi that characterized the findings in the patients who died after tracheotomy. In one other patient bronchoscopy done on the day before death showed edema of the glottis and lower larynx but no obstruction was encountered below the larynx. In view of the poor results that were being observed in other cases, tracheotomy was not done in this case and the patient later died suddenly with symptoms of acute obstruction.

In 4 other cases death occurred within the first 7 hours and in each instance the patient was moribund and in shock on arrival and failed to improve. In these patients coarse, bubbling râles were heard throughout the lungs from the time of entry. In the remaining 4 cases the respirations became increasingly labored although there was no marked stridor or evidence of obstruction other than that which resulted from the accumulated mucus in the pharynx. This mucus was raised only in small amounts and with great difficulty by the patient, and suction also failed to clear the air passages. In one of these 4 patients (Case 124) who died at this hospital 43 hours after the fire an autopsy performed at a military establishment showed an ulcerated laryngotracheobronchitis but there apparently was not sufficient edema to cause obstruction. The lungs in this case, however, showed diffuse necrotizing bronchopneumonia with numerous small areas of beginning abscess formation. The autopsy was performed by Dr. R. Castleman of the Massachusetts General Hospital who noted that this was the only one of 5 cases dying within 72 hours of the fire in which he found definite bronchopneumonia.

Extensive pneumonia was made out in only one of the patients in whom autopsies were done at the Boston City Hospital. This patient (Case 107) died on the seventh day and signs of pulmonary consolidation were made out for the first time on the day before she died. The lungs showed confluent areas of consolidation and the exudate in many areas contained a moderately large proportion of polymorphonuclear leukocytes. In Case 125 in which death occurred on the sixth day a similar process was beginning as evidenced by the finding of small numbers of polymorphonuclear cells in the serosanguineous alveolar exudate. The predominant cells found in this exudate, however, were monocytes. In the lungs of the other cases in which autopsies were done and in most of the areas in the lungs of the cases mentioned, the process was primarily one of necrotizing inflammation involving the air passages down to the smallest bronchiole. Accompanying this were scattered areas of congestion and atelectasis, and in many areas the alveoli were filled with viscid serous exudate containing fibrin plugs, red blood cells, histiocytes and plasma cells. In addition, there were thrombosed blood vessels and areas of infarction. •

The findings in these cases were interpreted at the time as being manifestations of severe laryngotracheobronchitis with areas of atelectasis and with diffuse infiltration of the pulmonary parenchyma, particularly in the lower and dependent portions, the exact nature of which was not entirely apparent. Autopsies, however, showed that there was widespread congestion, edema and laryngeal

in the lung with some scattered areas of atelectasis and some infarction. Areas of necrotizing bronchopneumonia were noted in addition in some of the cases but these were extensive and confluent only in Case 107, the patient who died on the seventh day. X-rays consistent with the clinical findings were obtained on the second day or later.

*Time of death of fatal cases and duration of hospitalization of the survivors*

The time of death in the 39 fatal cases is shown in table 4. The relative importance of the acute respiratory complications and the obstruction to the airways as a cause of death is seen from this table. To be sure, some of those in whom tracheotomy was performed may have succumbed as a result of their surface burns, particularly when 30% or more of the body surface was involved.

TABLE 4  
*Time of death in cases with and without tracheotomy*

TIME OF DEATH	TRACHEOTOMY		TOTAL NUMBER OF DEATHS
	Done	Not done	
First 6 hours	1	5	6
7-12 hours	1	3	4
13-24 hours	4	2	6
25-36 hours	5	2†	7
37-48 hours	0	3†	3
Third or fourth day	3	1†	4
Fifth, sixth or seventh day	1	2†	3
Second week	0	3	3
After second week*	0	3	3
Total	15	24	39

\* These deaths occurred at 28, 80 and 157 days, the first one occurring at another hospital 6 days after the patient was transferred there for skin grafting.

† One of these patients died of obstruction to the airways but tracheotomy was not done.

However, most of the deaths in the first 12 hours and almost all of those which occurred after the fifth day were not related to the obstructive phenomena, although pulmonary pathology may have contributed to these deaths.

In table 5 the average time of death and the length of the hospital stay of survivors are correlated with the extent of the surface burns and with the severity of the respiratory complications. In the cases with respiratory involvement of Grade 4 severity, the deaths occurred early—11 on the first day, 9 on the second day, 1 on the third day and the remaining 6 on the fourth to the seventh day. The average was somewhat less than 2 days. This is in contrast to the much longer average period of survival of the other fatal cases in whom the respiratory symptoms were not so severe. In the cases of Grade 4 severity there was no correlation between the period of survival in the fatal cases and the extent of their surface burns. Furthermore, only in that group did fatalities



occur in patients who had burns involving less than 30 per cent of their body surface (cf table 1) In cases with less severe respiratory complications deaths occurred only in those with extensive burns, that is 30 per cent or more

The average time of survival after the fire for all the fatal cases was 9 days If the cases of respiratory involvement of Grade 4 severity are excluded, the average duration of the fatal cases was 24 days It is fair to say that this speaks well for the general management of these severely burned cases in spite of the

TABLE 5

*Relation of the duration of hospitalization to the extent of the surface burns and to the severity of the respiratory complications*

PER CENT OF BODY SURFACE BURNED	GRADE OF SEVERITY OF RESPIRATORY INVOLVEMENT						All recovered cases
	0	1	2	3	4		
					Lived	Died	
0	4*	3		18†	23	1	6
1-4	2	9	16	15		1	10
5-9	53	27	31	38	43	2	36
10-19		60	135	83		2	94
20-29		142	155	120		1	140
30 or more							
Lived		283					283
Died	80	9	62	4		3	16†
All recovered cases	12	41	45	36	36	2‡	33

The numbers each represent the average number of days (to the nearest day) that the patients were kept in the hospital The numbers of cases represented in the different categories are shown in part A of table 1 10 patients were discharged or transferred to other hospitals within the first 18 hours and the subsequent hospitalization of these cases is not included 14 belong under respiratory Grade 0, 3 in Grade 1, and 2 in Grade 2 With respect to the surface burns 6 of these patients had none, 12 had 1 to 4% and 1 had 6%

\* Of 8 cases represented in this average, 2 were kept in the hospital because of bodily injuries (fracture and contusions) The average hospital stay of the remaining 6 cases was less than 1 day

† One case with burns of the larynx and vocal cords

‡ Fatal Cases The average duration of all the fatal cases was 9 days, excluding those with respiratory involvement of Grade 4 severity, the average duration of the fatal cases was 24 days

fact that only 2 of those with burns involving 30 per cent or more of their body eventually recovered Among the survivors the average period of hospitalization was directly proportional to the extent of the area involved in the surface burns In general, the duration of hospitalization was not materially affected by the severity of the respiratory damage except in rare cases

#### *Observations on vital capacity*

Determinations of vital capacity were made in 42 patients on the twelfth day and in 14 patients on the twenty third day At these times many of the patients

who had only minor burns and little or no respiratory tract involvement had already been discharged and most of the fatal cases had already died. The results of these determinations are summarized in the lower part of table 2. The results of subsequent tests are considered in the later section which deals with the follow-up studies.

The few tests done in the cases without respiratory symptoms all gave essentially normal values. Values ranging between 45 and 81% of normal were obtained on the twelfth day in 7 patients with mild respiratory symptoms (Grade 1). One of these patients had a coughing spell with each test at the end of deep inspiration and full expiration and another complained of pain in the chest at the end of inspiration. Three of the 7 patients with low values were re-tested on the twenty-third day and the vital capacity in 2 had returned to normal while in the third it was still 75% of normal. The latter was found to have a normal vital capacity when seen 2 years later.

Low values were obtained in 4 of the 10 patients with Grade 2 respiratory involvement tested on the twelfth day. These values ranged from 50 to 84% of the theoretical normal. One of these patients complained of pain and the other had some wheezing at the end of inspiration. The test was repeated on the twenty-third day in 3 of these patients and normal values were obtained in 2 of them while in the third the vital capacity was 82% of normal.

Only 4 of the 15 patients with Grade 3 involvement that were tested were found to have normal vital capacity when tested on the twelfth day and the values in the other 11 ranged between 25 and 88% of normal. The tests were not entirely satisfactory in 6 of these patients—3 of them coughed at the end of inspiration and expiration, 1 was markedly dyspneic (the vital capacity in this case was estimated to be 25% of normal), and 2 felt that they could not fully expand or deflate their chest. The vital capacity had increased appreciably in all 7 of those who were re-tested on the twenty-third day and in 3 of them it had returned to normal. Only 1 of the patients, Case 91, who had a tracheotomy was tested on the twelfth day and he was found to have a normal vital capacity at that time.

#### *Summary of the clinical aspects of the respiratory complications*

The clinical features of the respiratory complications in the 131 cases admitted to the Boston City Hospital from the Cocoanut Grove fire were described. In order to facilitate the description, the cases were divided into 5 groups according to an arbitrary but convenient classification based on the severity of the clinical manifestations. The cases were fairly well divided among these 5 groups. An independent classification was based on the extent of changes found in the X-rays of the lungs. Details of the X-ray findings are reported elsewhere (13). When the clinical severity of the respiratory symptoms was compared with the X-ray findings a close correlation was noted. The correlation was remarkably close when due allowance was made for the fact that the symptoms in many cases were much more severe than the objective physical findings.

There was quite a close correlation between the extent of the surface burns and the severity of the respiratory complications. In a number of individual cases,

however, there were wide discrepancies. Satisfactory or partial explanations were found for some of these discrepancies. Of particular interest is the striking fact that all of the deaths occurred in two types of cases—either, 1) those in which the burns involved 30% or more of the body surface or 2) those with the severest type of respiratory symptoms, particularly those with manifestations of marked obstruction to the air passages. Indeed, there were only 2 recoveries among 22 cases in the first category and only 3 recoveries among 30 cases with respiratory symptoms of Grade 4 severity.

Because of its interest in relation to the management of victims of the inhalation of pulmonary irritants both in gas warfare and in industrial accidents, the problem of the fluid balance during the first day was given separate consideration elsewhere (15). The large amounts of plasma used as well as the large volumes of fluid administered in some cases made this aspect of special significance. The amounts of plasma used varied primarily with the extent of the surface burns. The large average amounts used in the patients with the severer grades of respiratory damage was due chiefly to the extensive burns which they had. Detailed analysis of the data indicates that the pulmonary complications were probably not aggravated by the large volumes of plasma and other fluids that were used.

The general condition of the patients on their arrival at the hospital or shortly thereafter was considered to be good in most of those who were free of respiratory symptoms and in those with the lesser grades of respiratory involvement. The proportion of cases arriving in poor condition increased with the severity of the respiratory complications. The surface burns contributed to the poor condition in direct proportion to the extent and character of these lesions. This is also indicated in part by the fact that the number of patients who arrived in shock increased steadily with the increasing severity of the pulmonary involvement. The shock in most of the cases was attributable chiefly to the surface burns, although that was probably not true for some of the individual cases.

Evidence of smoke inhalation was obtained from the history or the appearance of the patient at the time of admission in almost all of the cases in which there were any respiratory symptoms. Considerable amounts of smoke, however, were probably inhaled chiefly by those with the severer grades of involvement.

As the severity of the respiratory complications increased, a greater proportion of the patients gave evidence of having lost consciousness while they were still in the burning building. Most of the patients regained consciousness rapidly after reaching the outdoors or while they were on the way to the hospital. A significant number of those with the severer grades of respiratory damage, however, were still either unconscious, stuporous or disoriented on arrival and remained so for some time in the hospital.

All of the symptoms and physical signs of respiratory tract involvement, as listed in Table 2 increased in frequency and severity in the cases with the progressive grades of respiratory involvement. Physical signs of pulmonary involvement were likewise more frequent and more extensive in the successive grades. The sputum was essentially of the same character in all of the groups, indicating perhaps that most of it probably originated in the upper respiratory tract, the trachea or major bronchi.

Fever was present in most of the cases in all of the groups, except among those who were entirely free of respiratory complications. Maximum temperatures of 104°F or higher, however, were encountered almost exclusively among the cases of Grades 3 and 4 severity. Terminal hyperpyrexia with temperatures reaching to 106° to 109° were encountered in 7 cases in the latter groups. Except in the cases with the severest grades of respiratory damage the fever was related chiefly to the surface burns.

A history of antecedent respiratory disease was obtained in 33 of the 74 cases from whom information in this regard was available. There was no relation between the recent or past history of respiratory infections and the occurrence or severity of the damage observed as a result of this fire. Only in an occasional individual was it considered likely that the symptoms were aggravated by a recent infection.

Tracheotomies were done in 18 cases among which there were only 3 recoveries. Most of these operations were done during the first 24 hours for increasing stridor and evidence of obstruction to the airways. In some it was done after the patient had stopped breathing and could not be resuscitated, in others relief was obtained but this was only temporary and death from obstruction occurred usually within the next 3 days.

Most of the deaths which occurred in the first 12 hours and those which occurred after the fourth day were directly or indirectly a result of the surface burns.

Various forms of local treatment of the surface burns were used in the present cases and some of them may have contributed to the fatal outcome in individual cases. These and related factors, however, are not within the province of this report.

The major respiratory damage in all of the cases may be described as laryngo-tracheobronchitis. In the severe cases the inflammatory reaction was intense and was accompanied by occlusion of various parts of the respiratory tree by a pseudo-membrane of fibrin and by viscid mucoid and sanguineous exudate. Pulmonary damage was also present in such cases and this consisted chiefly of congestion, edema and scattered areas of atelectasis, hemorrhage and pulmonary infarcts resulting from thromboses. Pneumonia occurred infrequently as small scattered necrotizing lesions and in only one case was there a large confluent area of pneumonia.

The average duration of the fatal cases was 3 days. In the cases with the severest respiratory damage death occurred early, while in those with the severest burns but with respiratory involvement of lesser severity the time of death varied considerably. Many died soon after arriving at the hospital while others died only after a prolonged period of hospitalization. In the patients who survived, the average period of hospitalization was 33 days, excluding all readmissions for secondary grafting. In general, the average length of the hospital stay was directly proportional to the extent and severity of the surface burns. This was not affected by the character or the severity of the respiratory complications except in isolated cases.

## ON THE POSSIBLE CAUSES OF THE RESPIRATORY TRACT DAMAGE

The relatively large number of victims of the Coconut Grove Fire in whom there was severe or fatal respiratory tract damage makes this a rather unusual disaster, particularly since there was no obvious source of any specific pulmonary irritant which is known to produce the type of lesion that occurred. The exact cause of death in the great majority of the victims who perished inside the burning building is not known since very few autopsies were performed. There were many, however, in whom there was little or no evidence of external burns or other injuries. A number of theories, therefore, have been advanced to explain this puzzling situation. Many of them have been reviewed among the theories on the cause and spread of the fire and fumes in the report by Moulton (16). Mention need be made here only of some which may have a direct bearing on the respiratory tract injuries.

*Incomplete combustion*

The building was air conditioned and, as might be expected, there was little access to air except through the ventilators. An air cooling system was located behind a false wall in the Melody Lounge where the fire started and so it presumably broke down early. The rapid spread of the flames among the numerous inflammable decorations, including those which covered the ceiling and other properties, may well have created a condition in which incomplete combustion was taking place. The various noxious gases which may be produced when such common materials as wood, paper, rubber insulations, wool and silk are burned in an atmosphere deficient in oxygen have been listed by Easton (19). They include carbon dioxide, carbon monoxide, some saturated as well as unsaturated hydrocarbons, hydrocyanic acid and methane. Evidence of carbon monoxide poisoning was obtained from a few chemical determinations as well as from the appearance of some of the fatal cases and of a few of those who survived. There is no reason to believe that any of these substances, however, produce inflammatory lesions of the respiratory tract like the ones observed here.

*Nitrous fumes*

The lesions in the lungs were reminiscent of those described among the victims of the Cleveland Clinic Disaster (20, 21) which resulted from inhaling nitrous fumes arising from burning nitrocellulose X ray films. Similar lesions have been described from exposure to flames and fumes of burning gunpowder (22, 23) or in other similar circumstances (24, 25, 26). The similarity was again brought out in a very striking manner when, some time later, a fatal case of surface burns and respiratory injuries resulting from burning nitrocellulose came under observation at this hospital. There was no evidence to implicate the burning of films or other nitrocellulose products at the Coconut Grove. The possibility of nitrous fumes arising from the "flame proofing" ammonium salts used on some of the furnishings was raised and dismissed because of the rather small quantities involved.

### *Phosgene*

Another theory which seemed quite plausible at the time concerned toxic substances which might have arisen from the escape of refrigerant gas. After the fire, some of the refrigerant tubing was found broken or melted. Holmquist (27) in a memorandum to the Office of Civilian Defense, called attention to the possible hazards which might result from damage to refrigerators and equipment in case of bombing. With respect to Freon, the refrigerant which was presumably used in the Cocoanut Grove's system, he pointed out that it decomposes to phosgene on coming in contact with very hot surfaces (and presumably with free flame). Ordinarily, however, he felt that conditions are not favorable for the production of dangerous concentrations of phosgene, because a fire will produce convection currents which will dissipate the gas. In this instance, the possibility that many persons might have been exposed to toxic concentrations of phosgene near the place where it was liberated and before it was dissipated, had to be considered.

Rumors to the effect that some victims who had no external evidence of injuries suddenly collapsed and died with pulmonary edema, lent some credence to the phosgene theory at the time. Further investigations, however, failed to corroborate those rumors, although pulmonary edema was described in some cases dead on arrival at the Massachusetts General Hospital (18). Moreover, among the cases studied at the Boston City Hospital, one outstanding feature in almost every case was the scant, thick and tenacious character of the sputum. This was true even in the cases with the severest respiratory damage and is in sharp contrast to the copious, frothy or watery pulmonary exudate usually described in cases of phosgene poisoning. Admittedly, the effect of external burns or of exposure of the body to high temperatures on this aspect of phosgene poisoning is not known.

One other point which seemed to discredit the phosgene theory was the reported failure to discover any evidence of fluoride etching of the glassware in the burned building or on the teeth of the victims. Hydrofluoric acid is the other substance which should have been released from the decomposition of Freon (dichloro-difluoromethane).

### *Fire gases and particles*

As an alternative and simpler explanation of the respiratory tract damage one need only consider the effects of prolonged inhalation of the very hot air and fumes which presumably contained many of the toxic products previously mentioned and, in addition numerous hot particles of fine carbon or similar substances contained in the smoke. Carbon-like particles were contained in the sputum raised for several days in some of the survivors and they were mixed with the exudate found in the trachea and in the large and small bronchi of the fatal cases. One may suppose that the severe respiratory damage would have been suffered by the ones who were exposed for a sufficient time, and hence, had to keep inhaling this mixture continuously before they reached the fresh air. Since carbon monoxide and other toxic gases were included in the mixture, the

same individuals should have had the greatest exposure to them and hence, they should have given evidence of their effects, at least temporarily Dr Allan Moritz and his associates are conducting experimental investigations of this aspect

### *Epidemiological investigations*

Toxicological and chemical investigations into the causes of the respiratory damage were not part of the present studies Because of the great interest in this aspect, however, an attempt was made to obtain information concerning any factors which might have contributed to the severity of the pulmonary lesions What may be termed an epidemiologic approach was used Each patient, when it was felt that reliable information could be obtained, was questioned concerning certain details of the fire In particular, data were obtained concerning the location of these patients at the time when they first became aware of the fire, their descriptions of the appearance and odor of the fumes, the amount they inhaled, the direction of their attempted escape from the building and when and where they lost consciousness Similar information obtained and recorded in the hospital records at the time of entry or later was also utilized

Information was obtained in this manner concerning 72 victims, including some who were with the informant patients but succumbed within the burning building Admittedly, such data are very crude at best Moreover, the least amount of information is available in the most important cases, namely, those who died of respiratory lesions either at the fire or soon after they arrived in the hospital Cases with respiratory tract symptoms of all the various grades of severity are represented, however, among the 72 cases in which information was obtained and there were 122 in whom data were available concerning the state of consciousness at the time of the fire and later A study of these findings together with the correlations between the severity of the respiratory symptoms and the extent and site of the surface burns revealed some points of interest

### *Relation of the respiratory damage to the surface burns*

It was shown in table 1 that there was fairly good correlation between the extent of the surface burns and the severity of respiratory damage Wide discrepancies could often be explained by special circumstances, as in the case of the bartender who covered his face with a wet bar cloth and sustained extensive burns of his body but his face was spared and he had no respiratory symptoms It was also pointed out that almost every victim who had respiratory symptoms also had burns of the face and nose These findings support the view that the respiratory irritant was directly related to the heat and flames of the fire as opposed to any specific pulmonary irritant independent of the usual products of combustion

### *Dispersion of cases with respiratory damage*

The "epidemiological" data obtained in 72 of the casualties are given in table 6 along with an estimate of the extent of the surface burns and of the grade of the

TABLE 6

CASE NO	LOCATION WHEN FIRST AWARE OF FIRE	PATIENT'S RECOLLECTION OF EVENTS		CONSCIOUSNESS		% BODY SURFACE BURNED	GRADE OF RESPIRATORY DAMAGE
		Fire and smoke	Direction and result of attempted escape	Leaving C G	Arrival B C H		
5	ML near stairs	Saw flames across bar & on stairs, inhaled little smoke	Upstairs, across lobby, rapid escape, in PX	C	C	6	1
11 <sup>a</sup>	Bar in ML	Saw flames start and spread upstairs, inhaled much thick smoke, ? odor	Upstairs, was burned on stairs, PX blocked, crossed MDR, out SX, returned to MDR, out SX, back to MDR	U	U	16	3
10	ML near stairs	Saw "burst of flame" across ML, inhaled much black, "choking" smoke	Upstairs, PX blocked, across MDR, trapped, crawled	C	C	2	3
17 <sup>a</sup>	ML near stairs	Flames burst across bar, inhaled no smoke	Led by firemen through SX, with girl who died in C G	C	C	30	1
22	ML near stairs	Flame behind bar, inhaled black smoke, ? odor	Upstairs, was trampled, crawled & pushed out PX	U	C	6	3
28 <sup>a</sup>	ML near stairs	Saw first palm catch fire, inhaled little smoke	Upstairs, PX blocked, across MDR, carried out SX	C	C	25	1
30	ML at bar	Saw flames and white smoke, ? odor, held breath	Upstairs, was pushed through PX	C	C	8	1
40	ML, with no 5	Flame "shot across room," white smoke, held breath	Upstairs, across lobby, through PX	C	C	1	0
63 <sup>a</sup>	ML across stairs	Saw fire, pulled coat over head, no smoke inhaled	Upstairs, across lobby, among first through PX	C	C	5	1
66	ML, with no 28	Saw flame and smoke, inhaled some	Upstairs, across lobby, was pulled out PX	C	C	1	2
67 <sup>b</sup>	ML near stairs	Saw flame & smoke, "held breath"	Upstairs, trampled in lobby, pulled out PX	C	C	11	1
90 <sup>c</sup>	ML	Saw flame, inhaled some black smoke	Upstairs, tripped in lobby, got out PX	C	C	5	4
109 <sup>a</sup>	ML	Saw flame, inhaled little black smoke	Upstairs, across lobby, got out PX	U	C	30	2, A0
33	In & out (fireman)	Wore "full service" mask	"Asphyxiated" in kitchen, extracted by colleagues	U	C	3	1
57	Kitchen (employee)	Saw flame, inhaled little smoke	Up service stairs, broke door, got out SX	C	C	3	1
2 <sup>d</sup>	Lobby at ladies' rm	Saw flame rise from ML, inhaled little smoke	Out revolving door at PX	C	C	5	0
4 <sup>e</sup>	Lobby at ladies' rm	Saw flame leap upstairs, inhaled fumes	To PX blocked, got half way across MDR	U	C	6	2
15	Lobby check room	Saw flame rise from ML, no smoke	Out PX, returned for coats, out PX	C	C	20	1
42	Lobby check room	Saw flames burst upstairs, no smoke	Across lobby, out PX	C	C	3	1
50	Lobby toilet	Retrospective amnesia	Did not get far, unconscious early	U	C	2	2
51	Lobby toilet	Flame from ML, inhaled much black smoke	Across lobby, PX blocked, across MDR, pulled out SX	C	C	28	2
59 <sup>f</sup>	With no 51	Saw flame from ML, felt intense heat	Across lobby, knocked down at PX, but pulled out	C	C	8	0
65	With no 50	Saw flame from ML, smoke felt like "taking gas"	To lobby, PX blocked, got half way across MDR	U	C	6	3



29	Middle of NCL	Saw flames and smoke inhaled some	To side exit tripped pulled out early by firemen	C	6	2
30	NCL bar	Flames hit him saw gray smoke ? inhaled none	Out side door out BX	C	2	1
31	NCL bar	Saw flames felt heat inhaled some smoke	Out and in BX 5 times dropped near door in NCL	C	55	1
32	NCL bar	Saw flames inhaled little flame or hot air	Across bar and NCL, out BX	C	3	0
33	NCL, with no 29	Saw flames and smoke ? inhaled none	To side door knocked down rose out BX	C	45	4
34	NCL, with no 30	Black bitter smoke covered face with wet bar tag did not see flame	Started for BX and got half way across	C	30	0
35	NCL, with no 31	Saw flames dark gray pungent smoke	To side door fell on floor others piled on him walked out BX when firemen lifted others off	C	45	3
36	NCL, with no 32	Saw flames smoke not seen or inhaled (?)	Got half way across to side door	C	45	3
37	NCL, with no 33	Surrounded by flames; inhaled much sweat smoke	To SX got a short way only	C	7	3
38	NCL, with no 34	Saw flames & black strong, irritating smoke	Out SX; returned to MDR pulled out rapidly	C	0	1
39	NCL, with no 35	Saw flames inhaled little black smoke	Got almost as far as SX	C	4	2
40	NCL, with no 36	Saw flames inhaled little black smoke ? odor	Out PY back to MDR through window over bar	C	5	3
41	NCL, with no 37	Saw flames then "everything got black"	Across MDR to SX was pushed out by no 8	C	1	1
42	NCL, with no 38	Saw flames "choked" by smoke	Pushed toward SX by no 13 was pulled out early	C	2	2
43	NCL, with no 39	Saw flames but no smoke	Toward SX, got near exit	C	4	3
44	NCL, with no 40	Saw flames all around inhaled much smoke	Into dressing room door to outside was locked	C	0	3
45	NCL, with no 41	Flames spread from lobby across MDR saw thick yellow & black smoke inhaled little odor of tar	Was pushed over railing to front of terrace	C	0	3
46	NCL, with no 42	Saw flames & black smoke from lobby	Across MDR through SX returned to MDR out BX	C	0	2
47	NCL, with no 43	Saw yellow flames inhaled smoke	To NCL; fell in passage was dragged out early	C	10	2
48	NCL, with no 44	Flames & smoke from ML overcome by 4 breathe	Across MDR out through SX	C	4	2
49	NCL, with no 45	Sheet of flames from ML inhaled little smoke	Toward SX got near exit	C	3	0
50	NCL, with no 46	Flames up from ML inhaled smoke ? odorless	Toward and through SX	C	3	1
51	NCL, with no 47	Inhaled much flame and smoke	Out SX returned to NDR extracted by firemen	C	6	3
52	NCL, with no 48	Flames shot up from ML inhaled little smoke	Toward lobby out through PY	C	5	1
53	NCL, with no 49	Flames about up from ML inhaled little smoke	Covered eyes rushed to SX did not get far	C	25	3
54	NCL, with no 50	Flames about up from ML inhaled black smoke	To SX trampled sprayed & extracted by firemen	C	10	1
55	NCL, with no 51	Heard shouting saw flame heat of fire hit him first was choked by smoke	Toward SX got near exit	C	13	2
56	NCL, with no 52	Saw flames at stairs inhaled much black, irritating choking smoke	Was knocked to ground rose climbed up on wall bar and got through window over bar	C	0	3
57	NCL, with no 53	Saw flames at stairs inhaled much black, irritating choking smoke	To NCL saw people piled at BX, was stampeded felt hose spray extracted by firemen	C	0	1

TABLE 6—Concluded

CASE NO	LOCATION WHEN FIRST AWARE OF FIRE	PATIENT'S RECOLLECTION OF EVENTS		CONSCIOUSNESS		% BODY SURFACE BURNED	GRADE OF RESPIRATORY DAMAGE
		Fire and smoke	Direction and result of attempted escape	Leaving C G H	Arrival B C H		
68 <sup>1</sup>	CB, near lobby	Saw flame rise from ML but no smoke	Found PX blocked, out window over wall bar	C	C	5	0
70	MDR, rear	Saw flames and smoke, inhaled much	Got only a few steps toward SX	U	C	2	3
77	MDR, rear	Saw fire, inhaled little smoke	To PX, trampled at door, was carried out early	C	C	0	1
91 <sup>c</sup>	MDR, middle	Saw flames rise from ML, inhaled much black smoke, odor like tar	Leaped up through a 2 foot ventilator, regained consciousness outside	U	C	6	4
110 <sup>a</sup>	MDR, rear	Saw fire, pulled coat over head	To PX, blocked, turned back, did not get far	U	U	29	2, A4
113	With no 19	Saw fire, inhaled much smoke	Started for SX, did not get far	U	C	30	3
3	MDR, beside stage near dressing room	Saw flames leap across MDR, inhaled much smoke	Into dressing room, lost & regained consciousness, saw many dead, extracted by firemen after breaking door	U	C	1	3
7	MDR, beside stage	Flames up stairs, thick, gray, irritating smoke	Leaped on CB, across MDR out BX	C	C	3	1
7 <sup>a</sup>	With wife (No 7)	Saw flames from ML, thick, irritating, blue smoke	Across stage and out BX (not admitted to hospital)	C	C	1	0
20	With no 3	Saw fire and smoke at distance, inhaled little	Rushed to SX and got out early	C	C	0	1
24	CB, stage end	Saw flame from ML, inhaled some smoke	Across MDR, out SX, got short way back in	U	C	14	3
26	MDR, near stage	Heard noise, saw flame & smoke, inhaled little	To lobby, blocked, across MDR, out SX	C	C	5	1
27 <sup>1</sup>	MDR, near stage	Saw fire, felt hot, inhaled little smoke	Stamped 10 ft from SX, dragged out SX by arms	C	C	0	1
46	MDR, near SX	Saw ceiling burst aflame, inhaled much smoke & flame	To SX, stampeded near door, extracted early by firemen	U	S	2	1
47	With nos 3 & 20	"Room burst into flame," choked by heavy smoke	Fell, others piled on her	U	C	0	3
53	Muscan, on stage	Saw no flame, saw and inhaled much smoke	To rear, outside door locked, back into MDR	U	C	1	3
55	With no 26	Heard shouts, saw flame & black smoke, felt choked	Started for SX, "gwooned," pulled out SX by no 26	U	C	5	0
69 <sup>m</sup>	MDR, near CB wall	Saw sheet of flame, inhaled thick, hot, black smoke	Toward SX with wife, place got dark, stampeded	U	C	0	3
74	With nos 3, 20 & 47	Saw flames & smoke in lobby, inhaled little	Directly to and out SX	C	C	0	1
92 <sup>c</sup>	MDR, in front of dressing rooms	Saw flames at distance, saw and inhaled much white, intensely hot smoke	Was pushed into dressing rooms, stampeded, extracted through rear door by fireman	U	C	0	4

Abbreviations: C = Coconut Grove, B C H = Boston City Hospital, ML = Melody Lounge, MDR = Main Dining Room, CB = Caricature Bar (in MDR), NCL = New Cocktail Lounge, PX = Piedmont Street exit, SX = Shawmut Street exit, BX = Broadway exit, C = conscious, U = unconscious, S = stuporous  
 a = clothes caught on fire, b = with another person who died at CG, c = tracheotomy case, d = wife died in Ladies' room, e = waiting for Nos 51 & 59, f = contusions of forehead & lost consciousness briefly outside CG. Man extinguished fire in hair, g = succeeded in getting his girl through PX uninjured, h = was with 4 people who died in CG, i = regained consciousness outside CG, j = husband was with her & died in CG, k = was with sister who died in CG, l = sustained contusions and abrasions when others piled up on her, m = with wife & 2 others all of whom died in CG

Nos 7, 7a, & 92 were entertainers

For definition of "Grades of Respiratory Damage" see page 224

A0, A4 refer to grade of pulmonary lesion at autopsy

respiratory tract damage The cases are arranged in groups according to the part of the building where they first became aware of the fire There were cases with each of the various grades of severity of respiratory symptoms in each part of the building This is seen more readily from table 7 There appears to be no correlation between the location where the persons found themselves and the amount of respiratory injury sustained

### *Extent of surface burns*

The extent of the surface burns varied considerably among those who were in the various parts of the building when the fire started The circumstances of their attempted escape accounted for most of the extensive burns which occurred These are noted in table 6 The route which each of the casualties took after they became aware of the fire and the points where some of them lost consciousness are plotted on the schematic diagrams of the Coconut Grove which are

TABLE 7

*Severity of respiratory involvement in relation to the location at the Coconut Grove where patients first became aware of the fire*

LOCATION AT COCOANUT GROVE WHEN FIRST AWARE OF FIRE	GRADE OF RESPIRATORY INVOLVEMENT					ALL CASES
	0	1	2	3	4	
Melody Lounge and kitchen	0	9	2	3	1	15
Lobby	2	2	2	2	0	8
Main dining room lobby end	3	6	10	7	1	27
Main dining room stage end	2	5	0	6	1	14
New cocktail lounge	1	4	1	1	1	8
Total	8	26	15	19	4	72

\* See figure 1

shown in figure 1 Many of those with extensive burns but with little or no respiratory damage had traversed one or more rooms but finally got out into the open air without losing consciousness within the building Others were stampeded and could not make good their escape Most of them sustained both extensive surface burns and severe respiratory injuries Still others, though they remained within the building, were protected from extensive surface burns by the bodies of others who had fallen upon them, but they continued to inhale the hot and irritating fumes and suffered severe respiratory tract damage if they lost consciousness before they were extracted and brought out into the open air

### *Relation of loss of consciousness to respiratory damage*

Perhaps the most significant finding was the rather close correlation between the loss of consciousness within the Coconut Grove building and the grade of respiratory damage This correlation in 122 cases is shown in table 8 Which among the various gases was responsible for the loss of consciousness is not known Presumably carbon monoxide contributed in many instances Simple anoxia and suffocation, and perhaps fainting may have been contributing factors

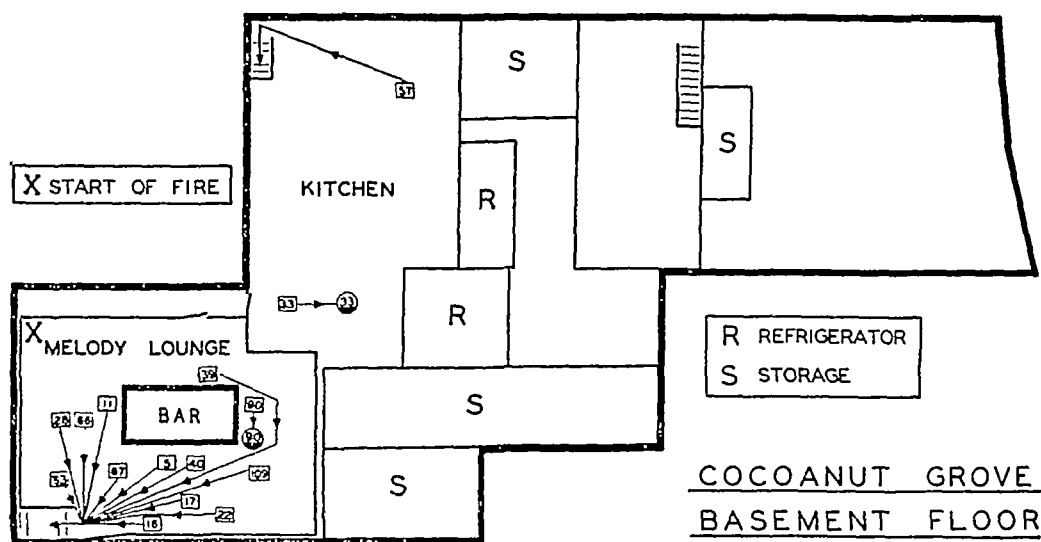
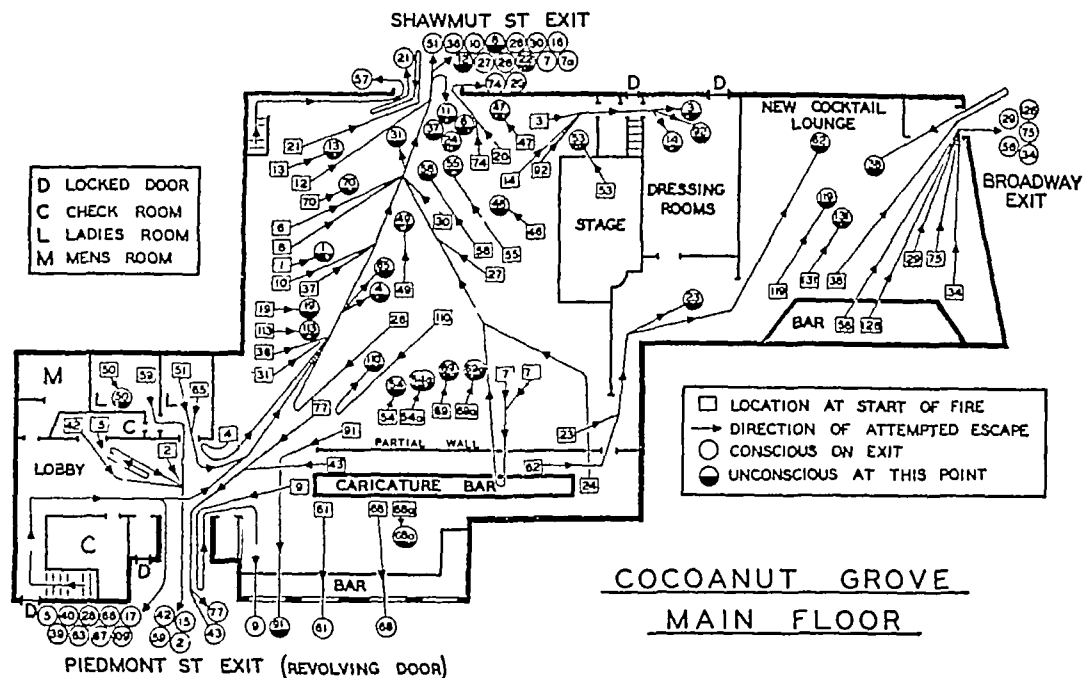


FIG 1 SCHEMATIC REPRESENTATION OF LOCATION OF THE PATIENTS AT THE TIME THEY FIRST BECAME AWARE OF THE FIRE AND THE GENERAL DIRECTION OF THEIR ATTEMPTED ESCAPE

The "Terrace" constituted the rear of the main floor dining room facing the stage. It was slightly elevated above the main floor and separated from it by a short railing. The "Dance Floor" was directly in front of the stage. (Drawing by A. Harriet MacDonald.)

TABLE 8

*Relation of the state of consciousness before leaving the Cocoanut Grove and the severity of the respiratory involvement*

STATE OF CONSCIOUSNESS	GRADE OF RESPIRATORY INVOLVEMENT					ALL CASES
	0	1	2	3	4	
Conscious	21	25	11	3	0	60
Unconscious	3	8	8	21	22	62

At any rate, it may be assumed that those who became unconscious had the greatest exposure and inhaled the largest amount of the hot, noxious gases from that time until they were extracted into the open air. They probably also inhaled substantial amounts before losing consciousness although some of them could recall taking only one or two breaths of the irritating fumes. No conclusions could be drawn as to the nature of the noxious gases from the descriptions given by the patients.

### *Conclusions*

On the basis of these crude observations and in the absence of other more definite information certain deductions may reasonably be made. There did not seem to be any concentration of casualties with severe respiratory tract injuries in any one part of the building. No clue has, therefore, been obtained as to any site where a respiratory irritant might have been released. The possibility that such an irritant may have escaped gradually but was dissipated rapidly with the currents of hot air and flames has not been excluded. The respiratory irritant was probably part of the hot air, fumes, and particles which resulted directly from the burning of the contents of the various rooms and rapidly permeated throughout all parts of the building. The fumes probably contained some poisonous gases other than those which contributed to the respiratory tract lesions. Those victims who inhaled sufficient amounts of these gases to render them unconscious, and those who may have lost consciousness from other causes before they reached the open air, inhaled the largest amounts of these hot fumes and particles and, therefore, sustained the severest respiratory tract damage. The amount and severity of the surface burns, on the other hand, seemed to depend primarily on exposure to free flames or hot surfaces.

### THERAPEUTIC PROBLEMS

While the surface treatment of the burns and the administration of the plasma and fluids constituted the major problems which engaged most of the attention of those concerned with the initial phases of the management of the Coconut Grove victims, there were many other therapeutic problems which were equally urgent and sometimes even more so. This was particularly true in the patients with severe respiratory tract involvement. Because of the unusual character of the cases encountered and the lack of previous experience with such cases, there were conflicting views at the time concerning the types of therapy indicated and the results obtained from the treatment employed. It is of interest, therefore, to review the data available with respect to the therapeutic agents and procedures actually used and to attempt to evaluate the results achieved in relation to the indications which prompted their use.

From what has already been said, this would seem to be an almost impossible task. The records of most of the cases were grossly inadequate for the purpose of studying the effects of most of the drugs used or of the procedures carried out. There were, however, sufficient numbers of cases in which bedside notes by doctors and nurses were made in some detail concerning the use and effects of some of these therapeutic measures. These notes supplemented by personal

TABLE 9

*Therapeutic agents and procedures used in the management of the victims of the Cocoanut Grove fire at the Boston City Hospital*

(Excluding the surface treatment of the burned areas)

Analgesics and soporifics	<i>Expectorants</i>
Opiates	Comp tinct benzoin (as below)
Morphine	Syrup of hydriodic acid
Codeine	Comp syrup of cocillana
Pantopon	Ammonium chloride
Dilaudid	Elixir of terpin hydrate
Others	Potassium iodide
Barbiturates	Other inhalation therapy
Phenobarbital	Steam tent
Pentobarbital	Comp tinct benzoin with steam
Amytal	Camphor, menthol and eucalyptol with steam
Seconal	Humidifier at room temperature
Pentothal	
Others	
Miscellaneous	Local therapy of the nose
Chloral hydrate	Mineral oil
Paraldehyde	Boric acid ointment
Aspirin	Azochloramide
Demerol	Ephedrine solution (drops)
Bromides	Amphetamine solution (drops)
Others	Sulfathiazole ointment
	Neosynephrine (drops)
For relief of anoxia	Local therapy of the oropharynx
Oxygen administered by	Suction and swabbing
Nasal catheter	Gargles
Nasal mask	Warm glucose solution
Oronasal mask	Warm corn syrup solution
Tent	Dobell's solution
Oxygen under positive pressure	Lozenges
By mask	Chloroform tablets
Through tracheotomy tube	Others
Helium oxygen mixtures	
	Fluids and electrolytes
For relief of respiratory obstruction	Human plasma
Tracheotomy	Human albumin
Suction	Glucose in distilled water, 5, 10 and 50 per cent solutions
Of pharynx by catheter	Sodium chloride, 0.85 per cent solution
Through bronchoscope	Alkalies
Through tracheotomy tube	Sodium bicarbonate
Through tracheotomy wound	Racemic sodium lactate
Postural drainage	Calcium gluconate
Artificial respiration	
	Sulfonamides
Antispasmodics, stimulants, etc	Sulfadiazine
Aminophyllin	Sulfathiazole
Theophylline	Sodium salts of above
Ephedrine	Sulfapyrazine
Atropine	
Adrenaline	Miscellaneous general therapy
Caffeine	Digitalis
Coramine	Adrenal cortical extract
	Desoxycorticosterone

observations form the bases for this presentation. A list of many of the various forms of therapy used in these cases is given in table 9. Those which will be considered here fall into 4 categories: 1) sedatives for the relief of pain, restlessness and insomnia, 2) procedures for the relief of anoxia and respiratory tract obstruction, 3) measures intended to relieve the local discomfort in the upper respiratory passages and 4) chemotherapy for the control of infection.

### *Sedation*

As pointed out by Beecher (28) with relation to the cases treated at the Massachusetts General Hospital almost all of the patients admitted to this hospital from the Cocoanut Grove fire required some sort of sedation immediately on arrival and for several hours or even days later. Almost all of them were restless and some were almost maniacal. Many factors contributed to this state but the chief ones may be mentioned briefly.

*Pain* undoubtedly was an important factor in many cases. In some of them it resulted from large distended blebs, and considerable relief was experienced when their contents were discharged. In others, the surface burns involved so many parts of the body that there was always some friction which was unavoidable due to pressure on one or more of the affected areas and which gave rise to considerable pain. The minor inflammatory reactions, particularly those of the eyes, nose, lips and throat, were very annoying and often quite as painful as the extensive burns of the skin.

*Fear, panic and hysteria* were major factors, particularly when the patients first arrived. This was inevitable in persons who had seen other victims on all sides, many of them dead or dying, and were naturally very apprehensive about their own condition and that of their friends and relatives. In some instances, particularly among patients who had comparatively minor injuries, rest and reassurance was all that was necessary, but most of the patients required more effective sedation with drugs.

*Anoxia and obstruction to the air passages* undoubtedly were the most important causes of the symptoms in those with severe respiratory tract involvement. The obstruction was often intermittent due either to spasm or to partial occlusion from exudate or from pieces of fibrin and desquamated epithelium and was almost always accompanied by extreme restlessness and at times by muscular twitchings or even convulsions. Coughing spells usually preceded and accompanied these manifestations but they were not always present nor marked.

*Insomnia* was another feature in the majority of the patients, particularly since there was considerable activity going on about the wards during the first day or so. Many of the victims were also having nightmares and hallucinations during which they were re-living their experiences. In still others the insomnia resulted from pain, breathlessness or apprehension.

*Morphine*. As might be expected, every type of sedation that was available in the hospital was used by one or another of the members of the staff and many of the patients received several drugs in rapid succession. Chief reliance in the first instance was placed on the use of morphine. The initial dose was given in

the admission rooms to almost every patient who presented any evidence of burns or appeared to be in any discomfort. The mechanism for its administration was adapted from the procedures advocated by the Red Cross and the Office of Civilian Defense for use in air raid casualties. The Medical Director of the hospital who took personal charge of general administrative matters within a few minutes of the arrival of the first patients, assigned a number of nurses to this task. They were each given a 10 cc syringe and sent to a nearby ward and asked to load the syringes with the solution of morphine sulphate from the ward supply. When they returned, they each proceeded to inject the amount prescribed by the admitting physician to each of the patients as they came along. The amount given was recorded on a conspicuous area of unaffected skin. Lipstick or any other available marking material was used for the purpose. The amount given at this time varied from 7.5 to 15 mg ( $\frac{1}{8}$  to  $\frac{1}{4}$  grain).

Additional doses of morphine and of other sedatives were given on the wards or in the operating rooms as they were deemed necessary by the physicians in attendance. The doses were repeated when they failed to achieve the desired result, particularly in cases with extensive burns or severe respiratory involvement or both. This may have been overdone in individual cases and may have contributed to some of the deaths that occurred during the first day or two. It was of interest, therefore, to analyze the total amount of morphine given in various types of cases during the first 24 hours. The data are shown in table 10. These figures were considered to be reliable since the morphine administered was probably recorded quite faithfully.

On the whole, larger doses were used in the fatal cases than in those that recovered. This was to be expected since the former included the cases with the most extensive burns or the severest respiratory symptoms or both. Only 2 patients who recovered received more than 60 mg of morphine in the first 24 hours. The largest amount was 90 mg in a patient who required 3 doses of 15 mg each within a period of 2 hours before he quieted down. The respiratory rate did not decline appreciably during the next few hours in this case. In a few patients who received large doses, other sedatives such as barbiturates by mouth or parenterally were given without effect before the opiate was repeated. Each of the patients was receiving oxygen, several were having frequent aspirations of their upper respiratory passages and a number of them required tracheotomy. These measures gave only partial or temporary relief, but often the first sedative effects of the drugs were noted only after these other procedures had been carried out to relieve obstruction and anoxia.

There were 2 patients in whom the respiratory rate was noted to become considerably depressed after doses of morphine which were probably excessive. One of them developed signs of obstruction and died shortly thereafter following an unsuccessful tracheotomy. The other suffered no ill effects but no further doses were given to that patient when the low respiratory rate was observed. This occurred during the second day and there was a general tendency to give less morphine after these experiences. There may have been others in whom respirations were depressed as a result of excessive amounts of morphine but in most instances the dyspnea and stridor continued. In one patient, for



example, 2 doses of 15 mg and 2 additional doses of 10 mg were given within a 12-hour period during which the respiratory rate continued to rise and the stridor and the râles in the chest increased

It is not certain that some patients were not harmed indirectly by suppression of respirations or of the cough reflex. The possibility is suggested by the fact that extensive lesions similar to those found in tracheotomized patients were also

TABLE 10  
*Analysis of the amount of morphine used in the first 24 hours*

TYPE OF CASES	NUMBER OF CASES	NUMBER WHO RECEIVED					AVERAGE AMOUNT
		15 mg or less	16-30 mg	31-45 mg	46-60 mg	61 mg or more	
Recovered cases—total	87	45	26	11	3	2	24
Severity of respiratory damage							
None	18	12	4	1	1	0	22
Grade 1	32	19	7	6	0	0	23
Grade 2	16	8	6	1	1	0	24
Grade 3	18	6	8	1	1	2	31
Grade 4 (tracheotomy)	3	0	1	2	0	0	35
Fatal cases—total	39	5	11	10	7	6	43
Tracheotomy not done	24	3	3	10	5	3	45
Tracheotomy done	15	2	8	0	2	3	40
Time of death							
Less than 12 hours	10	3	4	2	0	1	33
12-24 hours	5	0	3	0	2	0	39
24-48 hours	11	1	2	3	2	3	49
After 48 hours	13	1	2	5	3	2	48
All cases—total	126	50	37	21	10	8	30
Per cent of body surface burned							
None	12	8	2	1	0	1	25
1-9	74	38	23	7	3	3	25
10-29	18	4	8	4	1	1	33
30 or more	22	0	4	9	6	3	48

Excluded from this table are 5 patients who sustained neither burns nor respiratory damage, received no morphine and were discharged within a few hours

observed at autopsy in some patients whose symptoms did not seem to warrant an operation and in others in whom the obstructive symptoms occurred so rapidly that the patient succumbed before it could be undertaken. On the other hand, the large doses of morphine were almost always given only after it seemed impossible to control the patients' symptoms by any other means available at the time

A consideration of individual cases leaves the impression that more than

2 or 3 doses of 10-15 mg of morphine in a single day were probably unnecessary, that larger amounts were usually given in desperation and in spite of the fact that no obvious benefit resulted, that most of those cases had some evidence of obstruction and were not made more comfortable by this type of sedation and that some of the cases may possibly have been harmed by suppression of the respiratory reflexes and the consequent failure on the part of the observers to pursue the mechanical measures necessary to provide an adequate airway. It was further noted, by way of contrast, that when restlessness was due to pain alone smaller doses were required, relief was more rapid, was recognized more readily and lasted for longer periods so that it was not necessary to repeat these doses at short intervals.

*Other opiates* were used in a number of the cases. Pantapone in doses of 10 to 20 mg and dilaudid in doses of 3 mg were used off and on in patients with painful burns. In such cases they served the purpose as well as did the morphine. Demerol was used in only 2 patients with extensive burns and with only slight respiratory symptoms and they were relieved temporarily of restlessness by single or repeated doses. There were no real opportunities to appraise this drug in the present cases. Codeine in dose of 30 to 60 mg with or without additional analgesic drugs was used when coughing was severe and irritating. In some cases it was used from time to time as a substitute for morphine with varying success. Several patients with slight or moderate pain from burns or from irritation in the respiratory tract experienced relief from doses of 30 mg of codeine supplemented by 0.6 grams of aspirin. In many cases the opiates were given in conjunction with barbiturates, bromides or aspirin and the combined effect was usually better than that obtained from the opiates alone.

*Barbiturates* were used very freely, and probably every patient received them in one form or another. They were used most often and in the largest doses during the first 4 or 5 days. Phenobarbital and its sodium salt were used most frequently and pentobarbital sodium was also used in a large number of cases. In the patients with mild or moderate respiratory tract symptoms, doses of 0.1 to 0.2 grams given once or twice were usually adequate to relieve restlessness and permit comfortable sleep. Similar doses sometimes repeated every 6 hours failed to bring about this result in most of the patients with severe grades of respiratory tract involvement. Some of the latter received intravenous or intramuscular injections of 0.3 grams of phenobarbital sodium as many as 4 or 5 times within a few hours without being relieved of their restlessness. Such patients often quieted down very rapidly with only a single dose of this or other types of sedation after obstruction was temporarily relieved by suction or after some of the obstructing material in the trachea or larynx was dislodged and raised by vigorous coughing. As a matter of fact, it was mostly as an adjunct to the mechanical measures for relief of obstruction that the barbiturates and other sedatives seemed to have their greatest benefit by offering the patients more rest and some sleep after struggling vigorously for breath. The restlessness in patients with extensive burns but with only minor respiratory tract symptoms was variably affected. Some of those with painful lesions required

opiates as a supplement to the barbiturates in spite of large and repeated doses of the latter

It was difficult to determine the relative merits of the 2 barbiturates which were most frequently used. Pentobarbital in doses of 0.1 gram seemed to be somewhat more effective for the relief of insomnia and of lesser degrees of restlessness than phenobarbital in the same or somewhat larger doses, particularly in those with only mild respiratory symptoms. In those with severe lesions both of these drugs were often used in large doses but with less effect. Other barbiturates such as seconal and amytal were used in a few cases and gave results similar to those obtained with other forms. There was no definite evidence of untoward effects from any of the barbiturates unless the hyperactivity and hallucinations of some of the patients were manifestations of such reactions. The forms of sedation were sometimes changed in such cases. Suppression of respiration attributable to the barbiturates likewise did not occur.

*Other sedatives.* Chloral hydrate was used in only a few cases for insomnia. Paraldehyde was generally avoided. In 2 cases in which the latter was given intramuscularly in doses of 3 to 8 cc. it was noted as having no favorable effect but it did not seem to aggravate the respiratory symptoms. Bromides were used to supplement other sedatives particularly in persons who seemed emotionally upset, but this form of treatment was not pursued vigorously. Simple sedatives or analgesics such as aspirin, phenacetin and others were used quite liberally but by themselves failed to have any significant influence on the severe symptoms.

On the whole the barbiturates were effective for the relief of restlessness and insomnia in cases with mild or moderate burns and with minor grades of respiratory involvement. Large doses frequently repeated were required in cases with severe lesions. These were often unsuccessful until opiates were given when pain was the underlying cause of the restlessness or until anoxia was relieved by removal of an obstruction to the airways and by proper oxygen administration.

#### *Inhalation therapy for relief of anoxia*

*Oxygen.*<sup>10</sup> As in most general hospitals the amount of equipment available for administration of oxygen was limited. There were a few tents throughout the hospital, and only about one mask of the nasal or oronasal type was available on each of the adult wards. Within a short time after the patients reached the wards the need for oxygen treatment became apparent and all available means were mobilized for its administration. About one-half of the patients received oxygen during the first 1 to 4 days and some of them received it intermittently for several days longer, but, since many factors contributed to the patients' symptoms it was difficult to evaluate its effects. There were a number of features of the present cases which are worth recounting as illustrative of the problems which were confronted.

Because of the paucity of more suitable equipment the greatest reliance had to be placed on the ordinary rubber catheter of the urethral type. Difficulties

<sup>10</sup> We are indebted to Mr. Stuart C. Rand for making available a supply of oxygen equipment.

arose almost immediately. Most important was the objection on the part of the patient because of the marked irritation of the nose which was involved in almost every case with respiratory tract involvement of any degree. The mucous membranes in the nares were often burned or at least had become swollen and inflamed and later desquamated. There was a serous and bloody discharge which later became purulent. The openings of the nasal tubes frequently became obstructed so that the tubes had to be removed and cleaned or they were pulled out frequently by the patient who could not tolerate the irritations. In order to reduce the chances of the catheters becoming obstructed, the hard tip was usually cut off, the end smoothed out and a few additional openings were made in the terminal one-half inch of the tube. It was necessary also to avoid touching the inflamed posterior pharyngeal wall. Humidification of the oxygen was accomplished by passing it through a water bottle but there was an inadequate supply of proper equipment for that purpose. Dryness of the mucous membranes, therefore, probably added to the discomfort from the oxygen.

There were few instances in which striking relief resulted from oxygen given by nasal catheter alone. In many instances there was some improvement in the color of the patients but they complained bitterly and some of them actually became more restless because of the local irritation and struggled against retaining the catheters in place. In some of the patients the catheter was replaced by a mask, with some relief, but difficulties were then encountered because of the involvement of the face and lips. With the masks, however, it was sometimes possible to get enough relief so that, with the aid of sedation, the patient quieted down enough to obtain brief periods of rest. The few tents that were available were in constant use in the severest cases. They, too, had the usual limitations of that type of equipment, mostly the sensation of claustrophobia and the interference with nursing procedures.

Information concerning the effects of oxygen therapy was recorded in 47 cases in whom it was applied by nasal catheter. In only 9 was it considered to have given definite benefit. In 24 instances it either gave no demonstrable relief or was considered to have caused more discomfort than benefit. In the remaining cases the effects were doubtful. Oxygen by mask was recorded as giving relief in 4 cases while in 4 others it was not possible to continue with the treatment because of the objections of the patients. In the remaining cases the effects were equivocal or not recorded. Of 9 patients who were treated in a tent, some relief was experienced by 6, while the other 3 objected too strenuously to its use. None of these procedures, of course, attacked the major difficulty, namely, the obstruction which was responsible for the greatest amount of respiratory distress. They were helpful only when the airways were relatively free. In cases with obstruction there was either progressive dyspnea and stridor in spite of the oxygen administration or there were periodic violent episodes of air hunger either because of spasm or because of sudden lodging of exudate or membranous material in the larynx, trachea or larger bronchi. In such cases or during these episodes there was little or no benefit from the oxygen in any form and the patient usually struggled bitterly against all forms of apparatus. Only after

the obstruction was relieved by suction, or occasionally by an antispasmodic drug was it possible to resume the oxygen treatment with some success

*Oxygen under positive pressure* About 36 hours after the fire, Dr John H Evans of Buffalo, New York, President of the International Anesthesia Research Society, appeared at this hospital with a limited amount of equipment for the administration of oxygen under positive pressure and graciously offered his services in initiating and carrying out this form of treatment in a few of the very severe cases. The apparatus included the usual anesthesia mask with a large sized rubber bag which was kept inflated through a rather wide tube. A small but unmeasured amount of positive pressure was constantly maintained by the weight of a metal tongue which rested on the inflated bag. Unfortunately, this apparatus was quite bulky and may have been somewhat of a mental hazard to these patients most of whom were already quite apprehensive because of the limited success which attended their previous experiences with oxygen given through other types of apparatus.

Twelve patients received 100 per cent oxygen under positive pressure in this manner for varying periods;—some for only a few minutes and others intermittently over a period of 1 or 2 days. In 4 of these patients the mask was replaced by a tube inserted into the tracheotomy tube. Some of them had previously experienced temporary relief in various degrees from oxygen administration by tent or mask. In others the treatment was started during periods when the patient was having considerable distress.

It is not fair to judge the effects of this type of therapy from the results observed in these few cases. However, most if not all of those in attendance, were not quite as favorably impressed as was Dr Evans from their observations of this brief trial. Some degree of relief of acute respiratory distress became apparent within a few minutes in a few of the cases. In them, the cyanosis improved and possibly the amount of moisture in the lungs decreased as judged by the decrease in audible rales. These patients then quieted down enough to doze off under the influence of sedation which had previously been ineffective. In one-half of the patients, however, little effect was noted. At least one of the patients struggled violently while oxygen was being given under pressure and subsequently seemed to obtain more relief when oxygen was given through the ordinary nasal mask without positive pressure. In the patients who had previously had tracheotomies and in some of the other patients who subsequently died, the acute obstructive symptoms recurred in spite of the pressure-oxygen therapy. Only after suction was used did these patients obtain any measure of relief. The 6 patients who obtained some relief, however, did not have any true stridor or evidence of obstruction at the time. Under similar conditions other patients responded favorably to treatment with oxygen given in a tent or by a mask without positive pressure.

There was no definite clinical evidence of increased venous pressure observed in the patients while they were being treated with oxygen under positive pressure except as they became obstructed and began to struggle. Unfortunately measurements of the venous pressure and of the oxygen tension in the blood were

not made although they would have been of great value in estimating the benefits or possible harm from this type of treatment

*Helium-oxygen mixtures* were used in only 2 of the cases. Both were in very poor condition when the treatment was started and they were temporarily benefitted by it. The improvement in the color and in the character of the respirations was probably as great if not greater, than was observed in those cases who responded favorably to pressure oxygen. One of the 2 cases had had a tracheotomy earlier and both had evidence of carbon monoxide poisoning at entry. Both died in the middle of the second day with obstructive symptoms.

### *Relief of obstruction*

*Simple procedures* The relief of obstruction of the air passages constituted by far the most serious problem in many of the cases. Needless to say there was considerable difference in opinion at the time as to the best procedure to adopt when relief could not be obtained from inhalation therapy or from the use of other types of medication. In some cases the obstruction was due, in part at least, to a collection of secretions in the posterior pharynx that the patient was unable to raise. With a little cooperation it was sometimes possible to remove some of the thick material with the aid of moist cotton or gauze either on the finger or on the end of a tongue depressor. When the material was less viscid or frothy its removal could sometimes be facilitated by elevating the foot of the bed and turning the patient on his side. Usually these secretions could be removed only by suction applied either through a catheter attached to a syringe or with the aid of an electric suction apparatus of the type used during tonsillectomies.

*Tracheotomy* The laryngologists were best equipped to carry out the more drastic procedures. One or more of the members of their staff were available most of the time and they performed suction under direct vision through a laryngoscope or bronchoscope or through the tracheal tube. In the severest cases, however, obstruction often occurred quite abruptly, and at such times, it required the immediate attention of the first physician on the scene and he was usually one of the surgical interns or residents. When it was obvious that the obstruction was in the larynx or below, the decision to do a tracheotomy had to be made and carried out without delay. It is for that reason that the laryngologists actually carried out only a few of the tracheotomies. Some operations were undoubtedly averted by constant attention and by frequent aspirations. Others might have been more successful had they been done earlier and before complete obstruction occurred.

*Suction* The tracheotomies did not solve the problem satisfactorily in the majority of cases. This is understandable from the character of the lesions responsible for the symptoms. The fibrinous pseudomembrane and the desquamation of epithelium usually extended down to the smaller ramifications of the bronchial tree. Repeated aspirations were also necessary after the tracheotomy in all of the cases. This was done by inserting a catheter through the tube or through the wound and applying suction. In some cases a bronchoscope was passed through the tracheotomy wound and suction was performed under

direct vision. Suction was necessary just as frequently in the patient who received oxygen under pressure directly through the tracheal tube as in the other patients who were placed in a tent or were given oxygen through a catheter inserted into the tube.

One of the most striking aspects of the mechanical procedures just mentioned was the marked relief obtained in some of the cases in which the suction was successful in alleviating the obstruction. Large plugs of fibrin, pseudomembrane, blood and inspissated mucus were often dislodged and removed in such cases. These patients, who were quite exhausted by their previous experiences, would then readily respond to oxygen in any form with improvement in their breathing and in their color. Repeated doses of the various sedatives which previously failed to relieve their restlessness were now unnecessary. The patients usually relaxed and fell asleep aided perhaps by the previous sedation. The amount of rest and sleep which the patients then obtained depended upon how soon the obstruction recurred.

*Artificial respiration.* In a few patients artificial respiration was employed after tracheotomy and suction. At least one of the patients probably owes his life to this procedure which became necessary after one of the periods of obstruction and after the bronchoscopic manipulations which were done to remove some obstructing plugs. In 2 other severe cases, breathing was re-established after 15 to 30 minutes of artificial respiration but these patients died during the following day. In most of the remaining patients, however, the procedure was without effect. That was particularly true following tracheotomies.

#### *Antispasmodics and stimulants*

Because symptoms of obstruction occurred or became aggravated periodically, it was thought that spasm of the larynx, trachea or bronchi played a rôle, and for that reason antispasmodic drugs were used. *Aminophyllin* was used more frequently than other drugs because of previous favorable experiences with it in other forms of acute bronchospasm. Notes on the use of aminophyllin from which its effects could be judged were available in 30 patients, of whom 20 died. In all these cases it was given intravenously in doses of 0.25 to 0.50 grams, the former being repeated in some instances 2 to 4 times at varying intervals up to 4 hours. In addition, doses of caffeine were given intramuscularly in some of these patients. Most of them were having diffuse musical râles in the chest and various degrees of stridor. In none of them did the signs in the chest clear. In only one instance was there any improvement in the symptoms and in that case oxygen under pressure was given at the same time. Several of these patients were subsequently relieved either by suction or by coughing up some of the material which seemed to be the immediate cause of obstruction. In a few patients aminophyllin was given by rectum without benefit. No ill effects attributable to this drug were noted.

Observations on the use and effects of *ephedrine* were available in 16 cases. This was usually given subcutaneously or intramuscularly in doses of 25 to 50 mg. repeated at from 2 to 6 hour intervals for several doses. In only one instance

were any favorable effects on the obstructive symptoms noted after these injections. In several, however, there was a definite increase in the restlessness for one-half hour or longer after each dose. One-half of the patients who received this drug recovered.

*Atropine* is another drug which is often used in desperate cases, usually in the terminal phases when the pharynx and trachea are filled with mucus or frothy material which the patient is unable to raise. Most of the cases in which it was used in this series fall into that category. In a few cases of lesser severity atropine was given for excessive amounts of pharyngeal mucus to prevent the pain and irritation that accompanied efforts to expectorate. It was given in doses of 0.4 to 1.0 mg., the smaller amounts being repeated as often as every 4 hours for several doses in some of the cases. It was used almost exclusively during the first 2 days. Of the 36 patients to whom atropine was given 21 died, mostly in the first 4 days. In no instance was the desired effect achieved, and some of the patients actually felt worse following the administration of this drug. In a few instances the atropine was given in combination with ephedrine but that combination likewise did not have any favorable effect on the symptoms or on the objective signs in the chest. In fact, there was not one case in which appreciable "dryness" was observed as a result of these doses.

Other stimulants such as coramine, adrenalin and caffeine were also given. These drugs, too, were usually reserved for the final desperate stages when other methods failed. Most of the doses were given during the first day or two. There were only 5 recoveries among 24 patients in whom the administration of these drugs were recorded and their effects noted. They were not of any help under the conditions in which they were used.

#### *Expectorant drugs and inhalants*

It was previously noted that the sputum was usually thick, tenacious and scant during the first few days. In addition, the dryness of the upper respiratory passages was often aggravated by the oxygen administration. These facts, added to the inflammatory edema and soreness, made expectoration quite difficult and painful. Attempts were, therefore, made to alleviate this condition and to encourage expectoration, by the administration of the usual expectorant drugs and by humidification of the atmosphere with or without the addition of soothing agents.

The expectorants listed in table 9 are the ones most commonly used in this hospital. Each of them was used in from 10 to 20 patients in ordinary therapeutic doses and were usually started between the first and fourth day. When the desired effect was not obtained, either the dose was increased or a change was made to another agent. The general impression gained from the recorded observations was that most of the patients had some favorable effect from these agents but this was observed only after 12 to 24 hours or longer, and sometimes only after the dose was increased or the type of expectorant changed. It is not certain that the improvement observed would not have taken place without the aid of these expectorants. At any rate, the nurses' notes in more than two-thirds



of the cases indicated that expectoration began to be less painful and somewhat more copious and less tenacious from 1 to 2 days after this medication was started

Among the *inhalants* used the first to be tried in any significant number of cases was Compound Tincture of Benzoin administered in the usual manner with steam from a kettle of water placed near the bedside under a canopy which covered the patient. This was usually started during the second or third day in patients with irritated inflammatory lesions of the upper respiratory tract associated with sore throat and laryngitis. Among those in whom it was used were 3 patients who had had a tracheotomy including 2 who recovered. Improvement was recorded in all but 3 of the 24 patients in whom this form of treatment was used. Most of these patients volunteered the information that this treatment was very comforting, improved the hoarseness, relieved the dryness and made expectoration much easier. The relief usually began quite soon after the treatment was started. Similar effects were experienced by 3 patients in whom a mixture of camphor, menthol and eucalyptol instead of the benzoin compound was used with the steam.

In 12 patients there was an opportunity to try the effects of a *mechanical humidifier*<sup>11</sup> which saturated the atmosphere of the room without heating. Most of these patients, too, seemed to benefit by this therapy, at least temporarily. Some of them noted a definite change for the worse as the apparatus was turned off. In 2 of the patients, Compound Tincture of Benzoin was used in conjunction with this type of humidifier.

#### *Local therapy of the nose and oropharynx*

Perhaps the simplest and most useful procedures which added to the comfort of a large number of the patients were the local nursing measures designed to alleviate the irritation in the upper respiratory passages. Since all of the patients with respiratory tract involvement had burns of the mouth and nose, there was some nasal obstruction from inflammatory edema, exudation of serum, bleeding and crusting. The same was true of the lips and oropharynx. The nasal irritation was considerably aggravated when nasal catheters were used for oxygen administration. Purulent nasal discharges were usually observed after the third or fourth day.

The most effective measures were the simplest and gentlest ones. They involved light swabbing with cotton soaked in saline followed by application of bland substances such as mineral oil or boric acid ointment. These measures kept the surfaces moist and soft and prevented cracking. Applications of aqueous solutions of ephedrine, neosynephrine or amphetamine by drops or applied with a swab after the cleansing procedures sometimes gave considerable relief and permitted nasal breathing, at least temporarily, when that was not previously possible. They also helped to reduce the dryness of the pharynx.

In the mouth and throat, gentle swabbing with moist cotton or gauze was used to remove some of the thick mucous. Mild solutions of sodium bicarbonate

<sup>11</sup> Generously loaned by the Children's Hospital, Boston

were also helpful for this purpose. Large amounts of secretions sometimes required removal by suction. Some of the patients obtained some comfort from irrigations or gargles with warm solutions of glucose or of corn syrup. In a few patients analgesic lozenges containing small amounts of chloroform or anesthesin were used from time to time with slight relief.

### *Chemotherapy and control of infection*

Details concerning the use of chemotherapy in the present cases and an evaluation of the results have been presented elsewhere (14). Only a brief résumé of this aspect of treatment need be given here.

Sulfonamides, mostly sulfadiazine, were used in 76 cases including 15 fatal ones and all others in which there were severe burns or respiratory tract symptoms and who lived and remained in the hospital for more than 2 days. They were used primarily in the hope of preventing the spread of infection from the burned areas and to prevent or minimize pulmonary infections. The average dose was 60 grams given in an average of 11 days. Most of the sulfonamides were given orally, but parenteral injections of sodium sulfadiazine were used in 17 cases including 12 fatal ones.

There were many difficulties in administering these drugs and in maintaining a proper fluid balance, particularly because of impaired renal function resulting from shock or hemoglobinuria in those with severe burns. Alkalies were given at first because of the finding of hemoglobinuria, but these were used with caution. Blood levels tended to be high during the first day or so and low later on. Toxic effects were relatively infrequent, drug fever with or without rash occurred in 7 cases, renal colic in 1 and nitrogen retention in 3. The latter were all in cases in which hemoglobinuria and some nitrogen retention was demonstrated before the drug was started.

The results of the chemotherapy were difficult to evaluate. Fever occurred in almost all cases but was attributed to the burns when it occurred early. The same was true of leukocytosis. Infections of deeply burned areas occurred after the first week and were fairly frequent but not severe. Extension of the infection beyond the burned areas, however, was observed in only one case. *Staphylococcus aureus* was obtained quite frequently from the infected areas and was usually the predominant organism. Various gram negative bacilli and hemolytic streptococci were also cultured from many of the wounds. It was not possible to assess the significance of these organisms in relation to the healing of the wounds but the infections probably contributed to the malnutrition of some of the cases.

Pulmonary infections were few and usually mild, but extensive pneumonia was found in only 2 cases. Other patients had protracted respiratory symptoms and physical and X-ray signs in the lungs with fever and leukocytosis. It was difficult, however, to determine to what extent pulmonary infection was responsible for these manifestations since similar signs and symptoms were noted early in most of these cases. Furthermore, most of these patients had extensive surface burns, and infections in these areas probably contributed to the fever and

leukocytosis On the whole, it was considered that chemotherapy was responsible, at least in part, for minimizing pulmonary infection and for preventing delayed deaths from pneumonia in many of the cases

### Comment

It is apparent that the management of the respiratory tract complications in the victims of the Coconut Grove fire taxed the therapeutic skill and ingenuity of all those in attendance From the appearance of the lungs when they were seen *postmortem* one could readily appreciate the underlying cause of the symptoms and their severity as well as the failure of most of the measures employed Survival in the cases with severe damage obviously depended on the maintenance of a free airway by all available means The condition was quite analogous to that encountered in the severe types of acute laryngotracheobronchitis in infants and children (29), particularly when these conditions are associated with extensive membrane formation through the tracheobronchial tree All the known forms of treatment are far from satisfactory and the results are quite discouraging

The use of mechanical measures, including tracheotomy, for relief of obstruction to the airways was unavoidable in many cases The laryngoscopists were reluctant to perform tracheotomies They, of course, were best equipped to carry out the most useful procedures which could have averted those operations However, the high mortality rate following the operation does not seem to be an adequate justification for the failure to do tracheotomies since they were performed for the most part only after the other measures failed Possibly some of the deaths might have been averted if tracheotomy had been performed at an earlier stage and supplemented by frequent but gentle suction together with the application of other soothing measures when they were indicated The laryngoscopists should be constantly available at very short notice if tracheotomy is to be avoided Furthermore, the nature of the lesions was such as to require great care and gentle handling in order to avoid serious hemorrhage or further increase in the inflammatory edema as a result of traumatic procedures

The use of oxygen under positive pressure did not really receive a proper trial in these cases The types of apparatus now available (30) are much simpler and more efficient and also permit better control because it is possible to measure the amount of positive pressure Better results might have been attained had such apparatus been available and used more widely The introduction of ephedrine or neosynephrine or even adrenalin as a nebulized spray along with the oxygen might also prove helpful in such cases when used either with or without positive pressure (31)

The importance of keeping the respiratory passages moist by simple means cannot be overemphasized Attention to the hygiene of the nose and pharynx with irrigations, swabbing and the application of bland oils or ointments were most helpful in accomplishing this purpose Adequate humidification of the inspired air or oxygen is also highly important and was greatly appreciated by the patients. The use of expectorants given orally or added to the inhalants in

the form of Compound Tincture of Benzoin or some similar preparation seemed helpful to some extent and apparently contributed to the comfort of the patients. The beneficial effects of orally administered expectorants were considerably delayed and also less striking than those given by inhalation in a humid atmosphere.

Needless to say, cases of the type encountered offered numerous problems for investigation. Unfortunately, it was not possible to carry out some highly desirable studies on respiratory physiology and on the pharmacological effects of various therapeutic agents and procedures in the present cases. It is hoped that the account given of the problems which were encountered in the present cases will stimulate such studies by others who are properly equipped to do them. It is also to be hoped that considerable information which will prove useful in similar cases has already been acquired in the course of the numerous investigations which have been conducted in relation to chemical warfare and industrial medicine. The results of these studies when they become available, will undoubtedly clarify many of these problems and possibly offer new methods of approach to their management.

### *Summary and conclusions*

An account has been given here of the various measures used in the management of the respiratory tract complications in the victims of the Cocoanut Grove fire. The major problem and the one most difficult to overcome was the obstruction to the airways. This obstruction was due chiefly to a membranous laryngotracheobronchitis and in the severe cases yielded to nothing short of mechanical measures including bronchoscopic suction or tracheotomy. The failure of even these measures in many cases was due to the extension of the lesions along the smaller ramification of the bronchial tree.

In general, opiates were most successful in the relief of pain, the barbiturates were most useful for restlessness, anxiety and insomnia, and humidification of the inspired air, expectorant drugs, inhalants and local nursing procedures were most helpful in alleviating the discomfort in the upper respiratory passages. Oxygen therapy was of only limited value but its usefulness might have been greater had there been available more suitable equipment. None of these measures by themselves were of any value in relieving the symptoms which resulted from obstruction.

Chemotherapy with sulfonamides given systemically did not prevent infections of the burned surfaces but probably kept such infections from spreading and probably also minimized the complicating infections of the respiratory tract.

### FOLLOW-UP OBSERVATIONS

There was considerable speculation as to possible residual damage and sequelae which might result from the respiratory tract injuries in the victims of the Cocoanut Grove fire. An attempt was made, therefore, to determine to what extent symptoms and other evidence of respiratory tract damage persisted or developed among the survivors who had been treated at the Boston City Hos-

pital The information was gathered during a 26 month period following the disaster. Most of the follow-up studies were made at 3 intervals, namely, after 4, 9 and 26 months. In the first follow-up the information was obtained chiefly through a questionnaire sent to the patients and answered by them or by their physicians. At 9 months, the follow ups consisted entirely of personal interviews supplemented in each instance by physical and X-ray examinations. At 26 months, the information was obtained in a few instances by means of a questionnaire but in most cases by interview and examinations.

TABLE 11

*Occurrence of respiratory symptoms at various intervals after the Coconut Grove fire*

INTERVAL AFTER THE FIRE	GRADE OF RESPIRATORY INVOLVEMENT	NO OF PATIENTS	SYMPTOMS							
			Cough	Sputum	Dyspnea	Hoarseness	Hemoptysis	Chest pain	Nasal discharge	Sore throat
months	0	12	2	0	0	0	0	0	0	0
	1	23	6	1	0	0	0	0	0	1
	2	10	1	1	0	0	0	0	0	0
	3	15	3	0	0	1	0	2	0	0
	4	3	2	1	0	1	0	0	0	0
Total		63	14	3	0	2	0	2	0	1
0	1	9	0	0	1	1	0	0	0	0
	2	8	1	1	2	0	0	0	0	0
	3	10	4	1	1	1	0	0	0	0
	4	2	2	2	0	0	1	0	1	0
Total		29	7	4	4	2	1	0	1	0
26	1	13	3	2	0	0	0	1	0	0
	2	11	4	2	0	0	0	0	0	0
	3	11	6	5	0	0	0	0	1	1
	4	3	3	3	1	0	1	0	1	0
Total		38	16	12	1	0	1	1	2	1

\* See page 224

The occurrence of symptoms referable to the respiratory tract in various groups of patients and at the 3 different times when the observations were made is summarized in table 11. For convenience the cases will be considered in relation to the severity of the symptoms originally observed in the hospital and graded according to the criteria set down on page 224.

*Patients who were free of respiratory tract symptoms while in the hospital*

There were 12 patients in this group who responded to the questionnaire 4 months after the disaster. Eleven considered themselves to be in good health at the time and only one, Case 74, described his general condition as "fair" and

complained of fatigue and of a moderate cough which was non-productive. An X-ray of the chest taken by an outside physician at that time was reported as consistent with "pneumonitis." Only one other patient in this group, Case 89, complained of some cough which also was non-productive. There were no other complaints referable to the respiratory system in the patients of this group. There are no further follow-up observations among the patients of this group.

*Patients who originally had mild respiratory symptoms referable chiefly to the upper respiratory tract (Grade 1)*

Of the 23 patients in this group who replied to the questionnaire at 4 months, 22 considered themselves to be in good health while 1 described his general condition as fair. The latter had a non-productive cough and frequent sore throats. There were 5 others who had occasional cough which was either dry or was productive of only a small amount of green sputum in the morning. One of these 5 patients was also having frequent sore throats.

Nine of this group were interviewed and examined 9 months after the fire. Two (Cases 62 and 67) complained of tiring easily, 1 had slight dyspnea and hoarseness and the other 6 were in good health and free of symptoms. Only 2 of the 6 patients who had complained of cough at 4 months were seen at this time and both of them had become free of this symptom. Physical and X-ray examinations were negative in all 9 of these cases.

Data are available in 13 patients of this group 26 months after the disaster. Twelve considered themselves to be in good health and one, who was having frequent upper respiratory infections considered her general health to be fair.

The 3 patients who complained of cough at this time are of interest. One of them, Case 83, was a fireman who had frequent exposures to smoke and flame and had a chronic cough for many years. Another, Case 40, had no complaints at the time of the earlier follow-up but now had a mild non-productive cough of 1 month's duration. The third, Case 60, was one of those who had complained of cough at the 4 month's follow-up and continued to have a mild cough, chiefly in the morning, productive of a small amount of yellowish-green, non-bloody sputum.

None of the others had any complaints referable to the respiratory symptoms. Detailed system review supplemented by physical and X-ray examinations was negative in all of the cases. Vital capacity determinations were made in 7, including 3 who had low values when tested during the original hospital entry, and all 7 were found to be normal.

*Patients who had respiratory involvement of moderate severity (Grade 2)*

In this group 10 patients responded to the questionnaire at 4 months. All considered themselves to be in good health. Only one, Case 13, complained of a mild cough productive of small amounts of mucoid sputum in the morning.

Eight patients in this group were interviewed and examined after 9 months and all considered themselves to be in good health. One of those who had not

responded to the 4 month questionnaire, Case 58, complained of some dyspnea on exertion and a moderate cough, chiefly in the morning and productive of small amounts of mucoid sputum since discharge from the hospital. A second patient, Case 61, had frequent upper respiratory infections and a third, Case 30, complained of slight dyspnea on exertion. There were no other complaints referable to the respiratory system in these patients and a detailed system review was negative. Physical and X ray examinations of the lungs were negative in every case.

Data concerning 11 patients are available at 26 months and 10 of them described their general condition as good. The other patient, Case 58, considered herself to be only in fair health. She no longer had the persistent cough, sputum or dyspnea but she complained of an unusual number of upper respiratory infections. Four patients complained at this time of some cough which was dry or productive of small amounts of mucoid sputum mostly in the morning. Three of them had been followed earlier and had no complaints at the time of the previous follow ups. All other findings were negative except for the occurrence of jaundice in Case 52 which will be considered later. Vital capacity determinations were made in 5 of the cases at this time and all were normal.

*Patients who had severe respiratory symptoms (Grade 3)*

There were 15 patients in this group who replied to the questionnaire at 4 months. All of them had remained in good general health except one, Case 24, who had jaundice and will be discussed later. Three of these patients still complained of some cough: one, Case 1, had persistent hoarseness, a second, Case 16, was "always clearing her throat" and often "lost her voice" and a third, Case 4, complained of mild chest pain. One additional patient, Case 47, complained of chest pain.

At the 9 month follow up, 10 patients were seen and all were in good health except one, Case 69, who had jaundice and will be considered with similar cases later. Three patients, Cases 1, 3 and 4, complained of tiring easily. Hoarseness and cough were no longer present in Case 1, but the patient complained of some post-nasal discharge which she attributed to sinusitis. The frequent necessity for clearing the throat and the periods of aphonia were still present in Case 16 and, in addition, the patient had frequent sore throats and a dry cough. The chest pain had subsided in Cases 4 and 47. Three other patients complained of non productive cough. In 2 of them the cough had not been present during the first few months,—in the third, the cough was associated with slight dyspnea. There were no other symptoms referable to respiratory or other systems in these cases and the physical and X ray examinations were all negative.

Data concerning 11 patients in this group are available 26 months after the fire. At that time, 9 of them rated their general health as good and 2, as fair. One of the latter had no specific complaints. The other, Case 19, still complained of cough which for several months had been dry but had since become productive of about 100 cc of greenish sputum daily. This patient also had some chest pain with the cough and also had some post-nasal discharge. One

other patient, Case 8, who had not been followed previously had a cough productive of a moderate amount of sputum since the time of the fire but was otherwise well. No other complaints were noted and the physical and X-ray examinations were entirely negative. Vital capacity determinations were made in 5 cases at this time. Normal values were found in all of them, including 1 in whom a low value was obtained shortly after the fire.

#### *Patients who had been subjected to tracheotomy*

The 3 patients in this group who survived are of special interest and will each be considered separately.

*Case 90* This patient's general health has remained good. In response to the first questionnaire at 4 months she stated that she had no cough and raised no sputum. At both 9 and 26 months, however, she complained of a morning cough productive of small amounts of non-purulent sputum which occasionally was blood streaked. She has also been having slight dyspnea during upper respiratory infections but she had no asthmatic attacks since the fire. There were no other complaints referable to the respiratory or other systems. X-ray and physical examinations were negative and the vital capacity was normal on each of the last 2 occasions.

*Case 91* This patient, too, has remained in good health and he gradually returned to his original rather strenuous duties after only a brief period of convalescence. He complained chiefly of post-nasal discharge and some tenderness of the nasal mucosa. He also continued to have a slight cough productive of a small amount of greenish, non-bloody sputum. He had no other complaints referable to the respiratory or other symptoms. X-ray and physical examinations of his chest were negative. His vital capacity was normal at the time of the last follow-up but it had been normal before he left the hospital.

*Case 92* This patient replied to the 4 and 26 months questionnaire and was seen 2½ years after discharge. At 4 months she still had some hoarseness and a cough productive of a moderate amount of thick sputum which often "imperilled her breathing." After 26 months she had a slight cough but otherwise was in good general health and had no other complaints referable to the respiratory system. When last seen her general health was good and she had been back at work as an entertainer for over 2 years. She still had very slight cough and mucopurulent sputum, but this has steadily improved. She continued to have slight dyspnea and hoarseness after singing too long at a time. Her vital capacity was essentially normal as were the X-rays of her chest.

#### *Occurrence of jaundice*

Because of the many recent reports concerning homologous serum jaundice, and since large volumes of plasma and blood had been used at the Boston City Hospital in the treatment of the victims of the Cocoanut Grove fire, the occurrence of jaundice in 3 of these cases, 1 while still in the hospital and the other 2 after they had been discharged is of interest. The available details in these 3 cases will be presented briefly.



*Case 24.* This patient was a 26-year old white man who sustained burns involving 14% of the body surface, of which 10% were third degree, and also suffered severe respiratory damage (Grade 3). The surface treatment consisted of triple dye. He received 3,500 cc of plasma during the 2 months. During the eleventh week he began to have vague epigastric distress after meals and a few days later he became jaundiced. There had been no recent transfusions and no hemoglobinemia was found. For a few days his stools were almost clay colored and there was bile in his urine. His icterus index rose to 30 on the 83rd day. At that time his prothrombin concentration was less than 1% of normal. He was given daily intravenous doses of 10 mg of 2-methyl-1-4-naphthoquinone intravenously for 3 days but his prothrombin time did not return to normal for 6 weeks. During that time the icterus index had fallen to 10. Leukocyte counts remained about 7,000 per cu mm throughout his course. His total plasma protein concentration fell to 4.3 g per 100 cc of which only 1.0 g was albumin. Hippuric acid excretion was low and cephalin flocculation was abnormal during this time. Four weeks later, however, the plasma protein values and hippuric acid excretion were normal and the cephalin flocculation test was negative. The liver and spleen were never palpable and he was afebrile throughout this period. His subsequent course has been uneventful and he was discharged on the 130th day after the necessary skin grafting had been carried out. He has had no recurrence of jaundice or symptoms.

*Case 52.* The patient was a 25-year old office worker who had second degree burns involving about 2% of the body surface and moderate respiratory tract symptoms (Grade 2). The burns of the hands and leg were treated with triple dye. She was given 1,500 cc of plasma during the first 24 hours and received no further plasma or blood. She was discharged on the 17th day. About 5 months after the fire she noticed that her skin had become yellow over a period of 1 to 2 weeks. During this time she felt nauseated and had some vague abdominal discomfort. Her stools were light gray in color and her urine was dark at this time. She continued to feel poorly for about one month during which the jaundice gradually receded. The patient did not remain in bed and she had no medical attention during this time. There has been no recurrence.

*Case 69.* The patient was a 26-year old government inspector who sustained second degree burns of about 6% of his body surface and severe respiratory damage (Grade 3). The surface burns were treated with triple dye (4). He was given 1,250 cc of plasma during the first day and none thereafter. He was discharged on the 24th day and returned to work shortly thereafter. On March 5, the 97th day after the fire, he became ill with nausea and vomiting. Shortly thereafter, he noticed that his urine was dark and his stools light brown in color. Five days later he consulted a physician who told him he had "catarrhal jaundice." He remained in bed with jaundice, malaise and indigestion for about 2 weeks. He has been up and around since then but still had slight residual icterus and indigestion when seen here 2 months later. Shortly before that time he had an attack of severe, cramp-like epigastric pain occurring in spasms for 5 minutes each over a period of 48 hours but he has had no similar

attacks since then. There was no vomiting or recurrence of jaundice. He improved markedly after that and has been free of symptoms except for a slight cough. He has joined the Navy and when last heard from he had been on active duty for over 18 months.

### *Summary and comment*

From the data presented it is not possible to state the exact incidence of residual symptoms attributable to the respiratory tract injuries sustained at the Cocoanut Grove fire. Such symptoms were neither frequent nor severe. Persistent cough was the most common symptom. While most of the patients raised little or no sputum with the cough, particularly during the first few months, an occasional patient later began to raise copious amounts of mucopurulent sputum suggesting the development of bronchiectasis in those cases. Residual chronic nasopharyngitis and possibly the development of mild chronic sinusitis is suggested by the occurrence of post-nasal discharge in a few of the patients. Residual symptoms were more frequent among those who had the severest manifestations soon after the injury.

Jaundice, probably attributable to plasma injections occurred in 3 patients. These patients received 3,500, 1,250, and 1,500 cc of plasma during the first day after their injury and the symptoms of hepatitis began after 11 weeks, 5 months and 14 weeks, respectively. Only one of these patients had received injections of blood in addition to the plasma. The manifestations in these cases were similar to those of so-called "catarrhal jaundice" or of "homologous serum jaundice". Two of the cases were relatively mild while the third was moderately severe and had laboratory evidence of liver damage. All have recovered, apparently without residual.

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# THE CORONARY CIRCULATION

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The coronary vessels serve to carry blood for the nutrition of the cardiac muscle. Certain anatomic and physiologic features which distinguish the coronary circulation from that of other organs have made difficult the determination of the factors controlling the blood flow to the heart.

*Anatomically* the coronary circulation is unique in that numerous anastomotic connections exist between the coronary vessels and the ventricular cavities. Although under normal conditions these anastomoses are apparently non-functional, in pathologic states they may become important. The anatomy of the coronary circulation has been discussed in detail elsewhere. Briefly, the cardiac muscle is nourished by right and left coronary arteries which arise from the sinuses of Valsalva or just above the semilunar valves (195). The distribution of these arteries varies considerably from individual to individual. In general, however, the right coronary artery supplies the right auricle and ventricle, the sino-auricular node, auriculo-ventricular node and myocardial conduction system. The left coronary artery, which divides into a circumflex and an anterior descending branch, supplies the left auricle and ventricle. Both coronary arteries send branches to the interventricular septum. The division of the coronary arteries to supply the various cardiac muscle bundles has been described by Robb and Robb (169). The coronary arteries break up into progressively smaller arteries and arterioles and finally form a rich capillary network. The blood is then collected into coronary veins. The principal veins join to form the coronary sinus which drains into the right auricle. Other smaller veins empty directly into the right auricle. In addition, numerous small *Thebesian* vessels connect the capillaries directly with the cardiac chambers, and anastomotic sinusoids are present between arteries and arterioles, between capillaries and the cardiac chambers, and between arterioles and the cardiac chambers (199). A rich network of *lymphatic* capillaries is present which in the dog unites into a single trunk draining the entire heart (34).

The *nerve supply* to the coronary vessels is extensive. In the dog, cat, rabbit and guinea pig the larger arteries are supplied by both sympathetic and parasympathetic fibers in approximately equal proportions (214). The smaller vessels, however, are innervated principally by the parasympathetic system.

In general, the amount of blood reaching a tissue depends directly upon the pressure of the blood delivered to its capillaries (18). The blood is propelled by ventricular contraction, and the flow maintained during diastole by the elastic recoil of the arterial walls. This forward movement is opposed by the peripheral resistance to flow of the progressively smaller vessels through which the blood must course, and by the viscosity, or internal friction, of the blood itself.

*Physiologically* the coronary circulation is unique in that the peripheral resistance to blood flow varies throughout the cardiac cycle as the ventricular muscle contracts and relaxes. The flow reaching the cardiac muscle is therefore the resultant of a pulsatile inflow from the aorta, and a pulsatile peripheral resistance.

Differences in the anatomy and physiology of the coronary vessels among various species as well as among individuals of the same species have not been stressed adequately in the literature. Relatively few studies have been made of the human coronary circulation because of the obvious difficulties involved. Despite this, conclusions with regard to human coronary physiology have been drawn freely on the basis of experiments on lower animals. Furthermore,

knowledge drawn from studies of the isolated, denervated heart has been translated too readily to the human patient. The physiology of the coronary circulation has been reviewed critically from different points of view by Wiggers (210) and Anrep (2) and in a symposium of the American Association for the Advancement of Science (215).

#### MEASUREMENT OF CORONARY BLOOD FLOW

The measurement of coronary blood flow presents numerous difficulties. Investigation is complicated by the fact that under certain conditions blood can flow from the ventricular cavities directly into the coronary vessels through the numerous anastomotic connections present, and thus augment coronary arterial flow. On the other hand, the venous outflow from the heart is divided among a number of vessels, and the coronary flow cannot be determined accurately from the outflow of any particular one.

Many methods have been devised to determine the volume of coronary blood flow. The *outflow from the coronary sinus* was first used as a measure of total coronary flow by Morawitz and Zahn (152) who studied whole animals. The technique was adapted by Markwalder and Starling (142) to the heart-lung preparation in which the various determinants of coronary flow could be controlled separately. This method assumes that the sinus outflow is a fixed proportion of the total coronary blood flow. Early experimental work (47) suggested that this was true, but more recent studies (119, 121, 150) indicate that the ratio between coronary sinus outflow and total outflow is not constant. Coronary sinus outflow therefore cannot be used as a reliable index of total coronary flow.

A second method of measuring coronary blood flow is to determine the *outflow of the pulmonary artery* in a preparation in which the coronary vessels are the sole sources of blood to the right ventricle. This may be done by perfusing the coronary arteries of an isolated heart through a cannula in the aorta (47, 161, 132). The small quantity of blood which flows directly into the left ventricular cavity from small coronary vessels, an amount not exceeding three per cent of the total drainage of the coronary system (126), is ignored. Measurement of pulmonary arterial outflow is more accurate than measurement of coronary sinus outflow. Unfortunately it cannot be used in the naturally intact animal.

Coronary blood flow may also be determined by measuring *arterial inflow*. This may be done by measuring the flow from a reservoir perfusing the coronary arteries at a constant pressure (122, 130) or by interposing a flow meter in the course of the coronary arteries (10, 98). In the former method care must be taken that the measurement of arterial inflow is accomplished without any appreciable change in arterial pressure. In the latter method, the arterial flow may be measured either by cannulation of one or more arterial branches, or by the use of the thermostromuhr, a device not requiring cannulation. Techniques involving arterial cannulation can be applied only to acute experiments, and must necessarily disturb normal hemodynamic relationships. The minute coronary flow may be determined by perfusing a cannulated arterial branch at a constant

pressure (67), or more physiologically by means of the pulsatile outflow from the aorta. Thus Gregg and Green (88) measured the pulsatile coronary blood flow with an orifice plate meter, a device which records the drop in lateral pressure resulting from the passage of the blood stream through a narrow orifice. The larger the blood flow, the greater the drop in pressure which results. The blood flow can be determined by calibration. A simpler device, the rotameter, has been used recently by Gregg and his associates (98). This is a vertical, transparent tube of constant taper containing a freely movable float. The height of the float in the flowing stream is a function of the rate of flow, which can thus be determined after calibration. The device is said to have an error of less than 10 per cent.

For long term studies a method must be used in which changes of blood flow can be measured through an intact vessel wall. This was achieved by Rein (166) who used the thermostromuhr which applies heat to a blood vessel wall and to the blood passing through the lumen. The extent to which the unit heats the vessel wall depends upon the rate of blood flow which can then be determined by measuring the temperature of the vessel wall. In Rein's original instrument the blood vessel was heated by a high frequency alternating current. Calibration was difficult because of local heating of the vessel wall. Baldes and Herrick (10) were able to increase the accuracy of the thermostromuhr by using instead a direct current. They calibrated the instrument *in vitro* and claimed an error of no more than 10 per cent. The thermostromuhr can be placed around the coronary artery of a dog aseptically and left *in situ* for many weeks (39). Studies for as long as eight days after the insertion of the unit showed no changes in the electrocardiogram or femoral blood pressure of the dog (42). Gregg and his associates (91, 174) have criticized the thermostromuhr on the grounds that *in vitro* calibration is inaccurate and *in vivo* calibration accurate only for acute experiments in which no back flow occurs. None the less, the thermostromuhr is apparently an adequate meter with which to demonstrate qualitative if not quantitative changes in the minute volume of coronary arterial flow.

Under normal pressure conditions, measurement of arterial inflow is an accurate method of estimating total coronary blood flow. However, if coronary arterial pressure falls relative to right intraventricular pressure, the gradient of pressure between the coronary vascular bed and the ventricular lumen may be reversed. Then the ventricular muscle may receive part of its blood supply from the ventricular lumen, and the measured coronary arterial inflow will underestimate total coronary blood flow (122).

To determine the responses of the intact animal, the coronary flow must be measured *in situ*. This may be accomplished most accurately by measuring arterial inflow. The heart of the intact animal is under complex humoral and nervous controls. In the analysis of the factors which determine the volume of coronary flow in the intact animal, the heart-lung preparation, first used for the study of the coronary circulation by Markwalder and Starling (142), is invaluable. The effect on coronary flow of changes in cardiac output, aortic pressure intra-auricular and intraventricular pressure, heart rate and the physical and chemical properties of the perfusing fluid may be studied independently. The



coronary arteries may be perfused by the pulsatile outflow from the aorta, or the arterial branches may be cannulated and the coronary arteries perfused at a

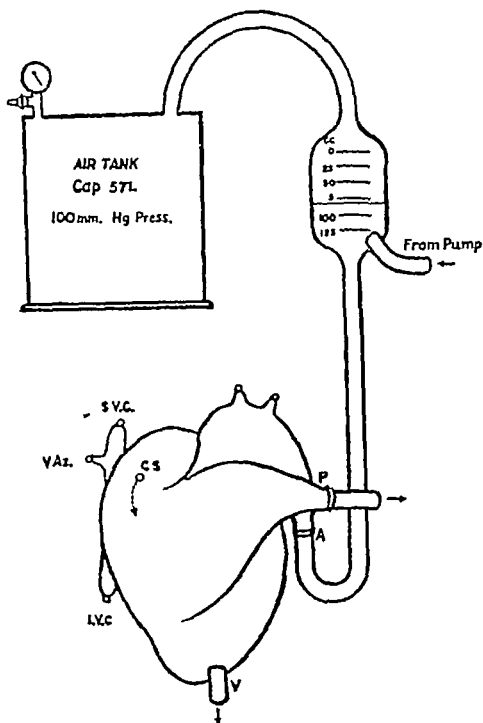


Fig 1 Modified Langendorff preparation for perfusing isolated fibrillating dog heart with defibrinated dog blood. Blood is propelled by a pump into the graduated reservoir whence, under constant temperature (35 to 37 C) and constant pressure of 100 mm Hg or more from the air tank it flows into the coronary arteries via the aorta (A). The innominate and subclavian arteries and the large systemic veins, superior (SVC), inferior venae cavae (IVC) and azygos vein (V.A.) are tied off. The coronary outflow from the sinus (CS) and Thebesian channels into the right heart is collected from a cannula in the left pulmonary artery (P) in a graduated cylinder and the flow timed with a stopwatch, the right pulmonary artery and lungs being tied off. A cannula (V) inserted into the left ventricular cavity serves as a drain for any Thebesian channels emptying into this chamber and as an indicator of the competence of the aortic valves. All blood collected is returned, after aeration, to the reservoir feeding into the pump.

KATZ, L. N., LINDNER, E., WEINSTEIN, W., ABRAMSON, D. I. and JOCHIM, K. Effects of Various Drugs on the Coronary Circulation of the Denervated Isolated Heart of the Dog and Cat. *Arch. Int. de Pharmacodynamie et de Therapie* 69: 399 (1938). Figure 1, page 402. Modified Langendorff preparation.

constant pressure. In the heart-lung preparation, coronary blood flow may be determined by measuring arterial inflow or, with much less accuracy, coronary sinus outflow.

The isolated heart is most suitable for the study of the effect of drugs on the caliber of the coronary vessels. Katz and his collaborators (126) use a modification of Langendorff's preparation (132) in which the coronary arteries are perfused through the aorta, the aortic valves preventing regurgitation of the perfusing fluid into the left ventricle. Others have cannulated and perfused the coronary arteries directly (106, 123). The coronary arteries may be perfused at either a constant or a pulsatile pressure (47) provided by a second heart. The latter more closely duplicates physiologic conditions but introduces another variable into the experiment. Blood flow is usually determined by measuring pulmonary arterial outflow. The pulmonary artery is open to the air so that the right ventricle meets no resistance in ejecting blood. The heart therefore performs no work in the expulsion of blood from the ventricle.

The importance of the composition of the perfusing fluid cannot be over emphasized. The coronary flow is affected by such physical properties of the perfusing fluid as temperature and viscosity as well as by its chemical composition. It is axiomatic that the closer the composition of the perfusing fluid approximates normal blood, the more likely will the results be applicable to the intact animal.

Finally, whether the heart is beating, quiescent, or fibrillating is of great importance. The beating heart is closest to the physiologic state. However, ventricular contraction seriously interferes with the interpretation of the action of a drug upon the coronary circulation. Thus, a decrease in coronary flow may be due either to vasoconstriction or to increased vigor of the heart beat, the latter increasing extravascular resistance to flow (2). In some studies this difficulty was avoided by stopping the heart chemically (106). For example, the heart has been perfused with non-oxygenated sodium chloride solution (207). As Katz and his associates (126) pointed out the perfusates themselves may alter the responses of the coronary vessels. However, when the heart is set into fibrillation, the ventricles no longer compress the coronary vessels rhythmically, changes in extravascular resistance are eliminated without changing the chemical composition of the perfusate.

#### NORMAL CORONARY BLOOD FLOW

*Total Coronary Blood Flow* The total blood flow through the coronary vessels may be determined directly by measuring coronary arterial inflow or pulmonary arterial outflow, or less accurately, by measuring coronary sinus outflow. It has also been calculated indirectly from an estimation of the work of the heart, the amount of oxygen required to perform this work, and the arterio-venous oxygen difference (111) all data difficult to obtain accurately. Although none of these methods is entirely satisfactory, under normal circulatory conditions measurement of coronary arterial inflow is most accurate. Values for the total coronary flow derived from studies of the isolated heart or heart-lung preparation must be viewed most critically, since these preparations are removed from normal nervous and humoral control and intraventricular pressure relationships are disturbed, particularly when ventricular fibril-

lation is present. With currently available techniques, the most accurate method of estimating total coronary blood flow would be to measure coronary arterial inflow in the intact and preferably unanesthetized animal.

As might be predicted from the diversity of techniques employed, estimates of total coronary blood flow through the quietly beating heart vary widely (210). Because of the relative accuracy of the methods used, the results of certain experiments seem more reliable. Evans and Starling (47) measured coronary sinus and pulmonary arterial outflow in the denervated isolated dog heart. At perfusion pressures of 100 to 110 mm. of mercury, the total coronary flow was 60 to 100 cc per 100 grams of heart per minute. Essex, Herrick, Baldes and Mann (40) reported a somewhat wider range of values for the coronary arterial inflow of the trained, unanesthetized dog at rest. They measured the flow through the circumflex branch of the left coronary artery with a thermostromuhr and, assuming that this represented 50 per cent of the total, calculated that total coronary flow was 76 to 176 cc per 100 grams of heart per minute. Comparable values were reported by Kountz and Smith (131) for the coronary arterial inflow of the human heart revived *post mortem*. They estimated that the coronary flow of a 300 gram normal heart perfused at a constant pressure of 80 mm. of mercury was 270 to 450 cc per minute. Since these revived hearts were removed from normal nervous and chemical control, these values may be too high, but they are probably of the right order of magnitude. The maximal possible flow has been estimated by perfusing human hearts *post mortem* with kerosene at a pressure of 100 mm. of mercury. For normal hearts the maximal possible flow is 31 cc per gm of heart per minute in individuals 40 years of age or younger but decreases with increasing age to 19 cc per gm of heart in individuals over 60. It must be emphasized that these values were obtained in a heart no longer beating and removed from normal chemical and humoral controls (33).

*Normal Distribution of Coronary Arterial Inflow* Studies of the distribution of coronary blood flow indicate that in the dog the right coronary artery receives about one fifth of the total inflow and the left the remaining four fifths. These values were reported by Anrep, Blalock and Hammonda (3) who perfused the right and the circumflex and descending branches of the left coronary arteries simultaneously at a constant pressure. Fifty per cent of the total blood flow went through the circumflex branch and thirty per cent through the anterior descending branch of the left coronary artery. Katz, Jochim and Weinstein (123) obtained similar results in the isolated, fibrillating dog heart, observing that the right coronary artery carried, on the average, 18 per cent of the total blood flow, the left circumflex branch 46 per cent, and the left anterior descending branch, 41 per cent, the total of 105 per cent was attributed either to experimental error or to the presence of functional collateral vessels in some preparations. These data were corroborated in the intact animal by Wégria and his associates (205) who measured coronary flow in the anesthetized dog's heart *in situ* with a thermostromuhr. They reported that the flow through the circumflex branch of the left coronary artery averaged 2.7 times the flow through the right coronary artery, approximately the same ratio observed by Anrep. We are not familiar with comparable studies on the human heart.

## FACTORS AFFECTING CORONARY FLOW

Numerous studies have been made to determine how the coronary circulation adapts itself to changing needs. The rate of blood flow through the coronary arteries is a resultant of several variables (122). Coronary blood flow depends directly upon the driving force of aortic pressure at the mouths of the coronary arteries. Flow is opposed by the resistance offered by the coronary venous pressure, by the viscosity of the blood itself, and by the smaller coronary vessels. The caliber of these vessels may be changed actively by changes in the vasomotor tone of the blood vessels or the chemical composition of the blood (2), or passively as the extravascular support offered to the intramural vessels by the cardiac muscle varies during systole and diastole.

*Coronary Arterial Blood Pressure* The blood flow through the coronary vessels is dependent directly upon the blood pressure at the root of the aorta. Measuring coronary sinus outflow, Markwalder and Starling (142) demonstrated this in the dog heart-lung preparation. It has been confirmed repeatedly in the intact animal (68), the heart-lung preparation (107) and the perfused heart (131) as well as in revived human hearts (2, 131).

In the intact animal, the pressure transmitted to the coronary vessels is not constant but pulsates, rising during systole and falling during diastole. Wiggers (210) has emphasized that coronary flow is not necessarily proportional to arithmetic mean blood pressure. During systole the forward flow of blood through the coronary vessels is impeded, particularly in the left ventricle, by compression of the intramural vessels produced by the contraction of the ventricular muscle. Smith, Miller and Graber (179), who measured coronary sinus outflow, thought coronary flow depended upon the diastolic level of blood pressure. Anrep (2) pointed out that this is substantially true if one means by diastolic pressure the average of the moment to moment variation in pressure throughout diastole. Actually, arithmetic mean blood pressure is a fairly good index of coronary flow, though Green and Gregg (68) observed that in the dog, coronary arterial flow, as measured with an orifice plate meter, rose proportionately less than mean blood pressure.

*Coronary Venous Pressure* If systemic venous pressure or right auricular pressure is elevated, one would expect *a priori* that the increased pressure would be transmitted to the coronary veins which empty into the right auricle, and that the resultant increase in coronary venous pressure would decrease coronary arterial inflow. Therefore, in mitral stenosis and in so-called right heart failure, the increased right auricular pressure might result in a decrease in coronary arterial inflow.

The influence of elevation of venous and right auricular pressures on coronary blood flow is difficult to study. An approach to the problem may be made by studying the effect of ligation of the coronary venous drainage on coronary blood flow. Repeated experiments on the heart *in situ* (80, 92) have shown that ligation of the coronary sinus or great coronary vein of the dog, which results in an increase in coronary venous pressure proximal to the ligature, is followed by a decrease in coronary arterial inflow. The decrease in flow occurs principally

in the left coronary artery, flow through the right being affected slightly if at all (92), both systolic and diastolic flows are decreased (80). In other words, as resistance to flow increases, coronary arterial inflow decreases.

When the coronary sinus or a large coronary vein is ligated, venous blood is diverted to other coronary veins and the Thebesian vessels. This limits the decrease in coronary arterial inflow in experiments in which one of these vessels is ligated (2, 150). This is also true to some extent in the heart-lung preparation in which right auricular pressure is elevated (2). Recent evidence emphasizes the importance of drainage through coronary veins other than the coronary sinus (97). This suggests that an increase in right auricular pressure in acute experiments restricts coronary arterial inflow more than is indicated by experiments in which the coronary sinus alone is ligated. However this may be ameliorated somewhat in the intact animal, for in the innervated heart-lung preparation an elevation of right auricular pressure is accompanied by reflex coronary vasodilation (63).

When the coronary sinus of the dog heart is ligated, the left ventricle shows marked venous congestion compared with the right, which remains relatively pink (82). This ligation performed *in situ* is not lethal and within 30 days peripheral venous and arterial pressures return almost to normal (190).

One might conclude that elevation of right auricular pressure such as occurs in mitral stenosis and congestive heart failure is accompanied by decreased coronary arterial flow. However, this is ameliorated to some degree by redistribution of venous drainage through such channels as the Thebesian veins, and perhaps by reflex coronary vasodilation as well. As a result, it may be that coronary arterial flow does not decrease early in the course of these syndromes.

**Heart Rate** The influence of heart rate on coronary blood flow has not been defined clearly. As Gregg (78) pointed out, one would predict that as heart rate increases, the minute volume of coronary flow would decrease. As heart rate increases, the duration of systole is increased relative to diastole. Since ventricular contraction increases peripheral resistance to flow, coronary flow during systole is less than during diastole. The minute volume of coronary flow should therefore decrease as heart rate increases and a greater proportion of each minute is occupied by systole.

To determine the effect of heart rate upon minute flow, the *true* mean perfusion pressure must be maintained constant (2). This is because at very slow heart rates not only is diastolic blood pressure low, but the length of diastole is so increased that true mean blood pressure is lower than would be predicted by averaging systolic and diastolic pressure arithmetically. The preparation should be denervated to eliminate confusing reflex effects. Preferably the heart rate should be controlled by electric stimulation. If the heart rate is changed chemically or by altering the temperature of the perfusion fluid or the sino-auricular node, these stimuli may affect the caliber of the blood vessels or the strength of ventricular contraction directly.

Reports of the influence of heart rate on coronary blood flow seem to reflect the range of rate studied. When rates are slower than the usual physiologic

range, coronary flow increases as heart rate increases. Thus Hausner and his associates (107) observed that in the dog heart-lung preparation, increasing heart rate from 32 to 71 beats per minute by electric stimulation increased coronary arterial inflow from 70 to 250 cc per minute as measured with a thermostromuhr. Through the middle physiologic range, alterations in heart rate are without notable effect on coronary blood flow in the dog or rabbit, whether measured in the isolated heart or heart-lung preparation (7, 8, 9, 106, 113, 122). In the intact dog, on the other hand, acceleration from 68 to 116 beats per minute was accompanied by a slight fall in minute coronary blood flow (77). Since the heart is innervated in these experiments, reflex changes may have occurred.

At more rapid yet still physiologic rates, minute coronary blood flow falls, as the relative duration of systole increases (2). Thus, coronary outflow from the right side of the isolated rabbit heart decreased when the heart rate was elevated to 180 beats per minute, not a remarkably rapid rate for the species (106). Similar results have been reported for the dog heart-lung preparation (7).

In the human heart revived *post mortem*, coronary blood flow decreased when the heart rate was accelerated by atropine, and increased when the heart rate was decreased by pilocarpine (130). Unfortunately the range of heart rates studied was not reported.

In general, then, the effect of heart rate on the coronary blood flow of the innervated heart depends upon the range of rate studied. At slow rates, acceleration increases coronary blood flow. At middle rates, alterations in heart rate are without effect on coronary blood flow. At rapid rates, an increase in heart rate decreases coronary flow. These changes are apparently modified reflexly in the intact animal. None the less, in the tachycardias encountered clinically, impairment of coronary blood flow occurs. In patients subject to angina pectoris, auricular or ventricular paroxysmal tachycardia readily induces pain provided the ventricular rate is 150 or higher (213).

**Temperature** Relatively few studies have been made to determine the influence of the temperature of the perfusing fluid upon coronary blood flow. If isolated strips of medium-sized coronary arteries are warmed from 18° to 37.5°C, they constrict, and if the temperature is further elevated to 45°C, they relax (28). The results of early experimental studies with isolated heart and heart-lung preparations were confused because changes in heart rate induced by the changes in temperature were not controlled (172, 154). When heart rate is kept constant, however, decreasing the temperature of the perfusing fluid below 39°C increases the coronary blood flow of both the dog heart-lung preparation (3, 7) and the isolated human heart revived *post mortem* (129). That is, lowering the temperature of the perfusion fluid increases coronary blood flow, an effect apparently due at least in part to coronary vasodilation. These experiments indicate the importance of maintaining the perfusion fluid at a constant temperature in studies of the coronary circulation. However, in the intact animal an increase in temperature is apparently of little importance. Diathermy over the precordial region sufficient to raise the temperature of the right ventricle of the dog from 96.2 to 104°F was without significant effect on coronary minus outflow (143).

*Blood Viscosity* The viscosity of the blood is a measure of the resistance to flow offered by the blood itself as a result of its internal friction. In most experimental studies of the coronary circulation, the vessels have been perfused with solutions of electrolytes, sometimes fortified with red blood cells, in relatively few has the perfusate been blood. Changes in the viscosity of the perfusing fluid however may alter seriously the volume of coronary blood flow. The importance of blood viscosity in determining coronary flow was studied by Gregg and Green (87) who measured coronary arterial flow with a constant pressure flow meter. When the heart was perfused with Locke's solution which is one fourth as viscous as whole blood, the minute volume of coronary flow was 3 to 4 times greater compared with perfusion of whole blood. The increased flow with Locke's solution occurred both in systole and diastole and presumably was due to the low viscosity, though slight anoxia may have been a contributing factor.

As Bazett (13) pointed out, changes in blood viscosity may be of considerable clinical importance. When the coronary arteries are partially narrow as by atherosclerosis, sudden changes in blood viscosity such as may occur in shock reduce coronary flow, and this may be responsible in part for the frequency of post-operative myocardial infarction.

*Anoxia, Asphyxia and Hypercapnia* The chemical composition of the blood is of great importance in determining the volume of coronary flow. Particular attention has been paid in the literature to the influence of the respiratory gases. *Anoxia* causes a profound increase in coronary blood flow. This has been observed in the intact anesthetized dog in which coronary arterial inflow was measured with an orifice plate meter (70) as well as in the isolated fibrillating dog heart (124), the dog heart-lung preparation (113) and the isolated rabbit heart (106). The anoxia was induced either by lowering the oxygen content of the coronary arterial blood or by preventing the utilization of oxygen by injection of sodium cyanide. In the dog heart-lung preparation (113) maximal dilation of the coronary blood vessels was reached when the arterial saturation fell to 20 per cent of normal, and in the intact animal, when the oxygen content of the inspired air fell from 21 to 7 per cent, a concentration at which the arterial blood is approximately 50 per cent saturated with oxygen.

*Asphyxia*, in which the carbon dioxide content of the blood increases and the oxygen content decreases simultaneously, is also accompanied by a great increase in coronary flow (70, 98). In the anesthetized but otherwise intact dog the increased flow is observed during both systole and diastole and precedes the increase in aortic pressure and decrease in heart rate which also occur. The increase in blood flow in asphyxia is probably primarily the result of anoxia rather than of the increased carbon dioxide content of the blood. In the isolated human heart revived *post mortem* (130) and the dog heart-lung preparation (113, 142) an increase in carbon dioxide content of the perfusion fluid moderately increases coronary blood flow. In the intact dog, however, the addition of 5 to 8 per cent carbon dioxide to the inspired air until slowing of the heart, premature systoles and a decline in aortic pressure occurred was without significant effect on coronary arterial inflow, measured by the orifice plate meter (70). Possibly in the

intact animal, reflexes prevent the increase in coronary blood-flow with hypercapnia. The coronary vasodilation observed with hypercapnia in the isolated heart or heart-lung preparation may be due to an increase in the hydrogen ion concentration of the perfusate, which of itself will increase coronary blood flow (37, 113). In the intact animal, the blood buffers may prevent any significant shift in blood hydrogen ion concentration.

The mechanism by which asphyxia and anoxia increase coronary blood flow is not clear. Presumably metabolites accumulate as the result of failure of aerobic oxidation (142), but the nature of these substances is unknown. Greene (75) has reviewed the effects of various tissue extracts, all of which lower arterial blood pressure and increase coronary blood flow. Adenosine, adenine and adenylic acid, breakdown products of nucleic acids, increased the coronary blood flow of the isolated dog (210), rabbit (200) and cat (201) heart, the human heart-lung preparation (2), and the anesthetized (203) and unanesthetized (46) intact dog's heart *in situ*. These metabolites, chemically related to the xanthines, presumably cause vasodilation (75). In addition, in the intact animal such extravascular effects as weakening of the ventricular-contraction and changes in heart rate and blood pressure may contribute to the increased flow.

In summary, asphyxia results in a profound increase in coronary blood flow. Anoxia is probably the primary element causing this increase, with hypercapnia playing a minor rôle. The mechanism of the increase in blood flow is not clear, but may be related to the accumulation of metabolites which cause vasodilation, as well as to changes in the strength of ventricular contraction, the heart rate and blood pressure.

*Cardiac Output* In the denervated heart, coronary blood flow is independent of changes in the total cardiac output as long as heart rate and true mean arterial pressure are constant. First demonstrated in the dog heart-lung preparation by Markwalder and Starling (142), this has been confirmed repeatedly by measuring coronary sinus outflow (9, 113, 154) or coronary arterial inflow (107). That is, coronary blood flow is unchanged by alterations in cardiac output as long as the resistance against which the ventricles contract is unaltered. As we shall see, reflexes modify this in the normally innervated heart.

*Extravascular Pressure* Repeated reference has been made to the resistance to coronary flow offered by the contracting ventricular muscle. *A priori*, the pressure developed during systole within the layer of muscle closest to the ventricular cavity should be greater than that within the lumen. Since left intraventricular pressure is considerably higher than right, left intramyocardial pressure should likewise be higher than right. The arterial supply to both ventricles is derived from the aorta, and the blood reaches each ventricle at a little less than aortic pressure. Therefore, relative to intramyocardial pressure, the arterial pressure within the right ventricle should be higher than within the left, and during systole the blood should meet more resistance to flow in the left than the right heart.

The actual force developed by the contracting muscle is difficult to measure. Gregg, Eckstein and Fineberg (85) reported that the systolic intramyocardial pressure of the left ventricle exceeded by a small amount the simultaneously



recorded intraventricular pressure. However, they themselves were dissatisfied with their technique (84, 85). Johnson and DiPalma (118) demonstrated that the pressure exerted on the intramyocardial vessels during systole varies at different depths within the ventricular wall. The extravascular pressure exerted upon an artery deeply imbedded within the ventricular muscle is much greater than that upon a superficial vessel. This is most important in interpreting studies of variation in coronary flow during the cardiac cycle.

Although measurement of intramyocardial pressure is difficult, the pressure within the ventricular cavities may serve as a rough index. Anrep and Hausler (6) measured coronary blood flow in the dog heart-lung preparation in which the coronary arteries were perfused at a constant pressure. Elevation of aortic pressure, and therefore presumably of left intraventricular and intramyocardial pressure as well, was accompanied by a decrease in coronary blood flow. The decrease occurred entirely during systole. In other words, as the resistance offered by extravascular muscular contraction increases, coronary arterial flow decreases. The converse is likewise true, a decrease in myocardial extravascular resistance is accompanied by an increased coronary arterial inflow. This has been confirmed by Katz, Jochim and Bohning (122) in the dog heart-lung preparation and isolated heart. As Gregg and Shipley (95) emphasized recently, these studies were made on denervated preparations. In the intact animal there are reflexes which oppose this paradoxical decrease in blood supply as the work of the heart increases.

When *ventricular fibrillation* occurs, intraventricular and presumably intramyocardial pressure fall to zero. As might be predicted, since extra-vascular peripheral resistance is sharply reduced, ventricular fibrillation is accompanied by an increase in coronary flow (7, 106, 113). *Auricular fibrillation* is apparently without effect on coronary blood flow (2) except in so far as changes in the rate and strength of ventricular contraction occur (7, 148).

*Change in Coronary Flow during the Cardiac Cycle* The blood supply to the ventricular muscle varies from moment to moment throughout the cardiac cycle. This variation in flow has been the subject of intensive study, the results of which have been reviewed ably by Anrep (2), Wiggers (210) and Gregg (78). The blood flow through the coronary capillaries themselves has not yet been measured directly. Instead the pattern of flow through the ventricular muscle has been inferred from studies of the phasic variation of arterial inflow and venous outflow during the cardiac cycle. Apparently arterial inflow is a more accurate index of intramural flow than venous outflow, though certain difficulties are inherent in its measurement. During diastole, the elastic recoil of the larger arteries tends to increase intramural flow, but at the same time the flow measured in the artery decreases. The more distally flow is measured, the less important this effect becomes. Moreover, measurement of the phasic variation in arterial inflow does not take into account differences in peripheral resistance among the smaller coronary vessels. Those on the surface of the heart are subjected to relatively little external pressure so that systolic blood flow is not sharply impeded. On the other hand, the intramural vessels are

compressed by ventricular systole to a varying degree depending upon their depth within the muscle (118) However, the arterial inflow actually measured is the sum of the flows into both superficial and deep vessels

The first modern studies of phasic variation in coronary flow were made by Anrep, Cruickshank, Downing and Rau (4) who measured coronary inflow and outflow with a hot wire anemometer In this apparatus a wire of low heat capacity is set into the neck of a perfusion bottle and its temperature is raised to a dull red heat Because of its low heat capacity, the wire is cooled very rapidly by small currents of air Changes in temperature of the wire change its electrical

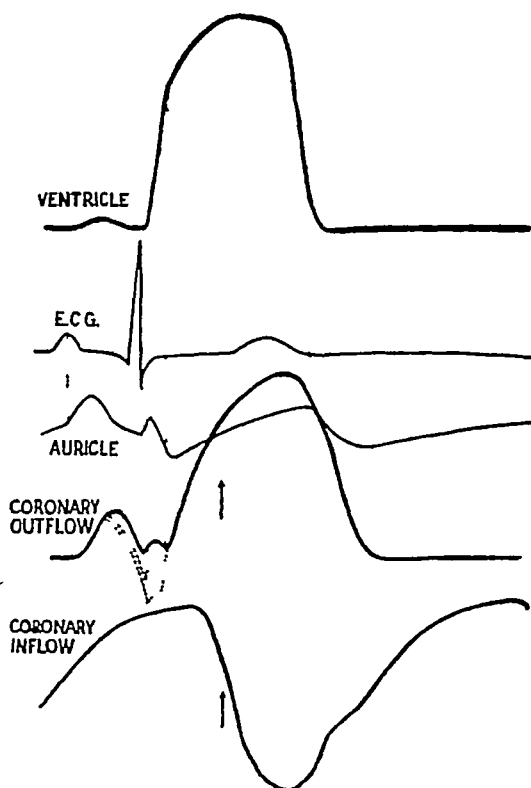


FIG 2 The relation of coronary outflow and inflow to other events of the cardiac cycle The augmentation of outflow and inflow are shown in both cases by a rise of the curve

ANREP, G V, CRUICKSHANK, E W H, DOWNING, A C AND SUBBA RAU, A The Coronary Circulation in Relation to the Cardiac Cycle Heart, 14, 111 (1927) Figure 4, The relation of coronary outflow and inflow to the other events of the cardiac cycle

resistance The hot wire is one arm of a Wheatstone bridge, and the changes in resistance are recorded by a string galvanometer As blood flows out of the perfusion bottle, air enters through the neck, cooling the hot wire Thus the amount of blood leaving the bottle can be determined accurately with an error of only 2 to 5 per cent The apparatus can be used equally well to determine coronary outflow, the displaced air cooling the wire as the bottle fills The hot wire anemometer can measure rapid changes in flow, though a slight lag occurs for which correction must be made However, as Anrep pointed out, "hot wire registrations cannot be used when the flow varies in both directions since in

whatever direction the air current proceeds the cooling of the hot wire will always be registered by a deflection of the galvanometer in the same direction (4) "

Anrep and his collaborators (4, 6) studied phasic variation in coronary arterial inflow in the dog heart-lung preparation. The coronary arteries were perfused through the aorta at a constant pressure maintained at a higher level than intraventricular pressure (Fig 2). During systole, inflow diminished rapidly, reaching a minimum when ventricular contraction was strongest, at the end of the ejection phase just before the dicrotic notch. In early diastole, coronary inflow increased, rapidly at first and then slowly, reaching a maximum at the end of diastole. When the heart beat was weak, the flow remained maximal throughout the isometric contraction phase of early systole, but when the beat was strong, diminution in flow began during the isometric phase. When ventricular contractions were strong, as would occur when the aortic pressure was high, the systolic diminution in flow was considerable. In the left ventricle a strong contraction sometimes completely arrested arterial inflow and when adrenalin was given, back flow into the perfusion bottle sometimes occurred. When ventricular contraction was weak, as with low aortic pressures, systolic flow was considerably higher. Green and Gregg (67) have confirmed these experiments for the most part for the dog heart *in situ* in which the ramus descendens of the left coronary artery was perfused at a constant pressure slightly less than aortic systolic pressure. However, in none of the experiments which they reported was the forward flow of blood completely arrested during systole.

In these experiments the coronary arteries were perfused at a constant pressure. Normally, however, the coronary arteries receive a pulsatile inflow from the aorta. Anrep, Davis and Volhard (5) investigated coronary arterial inflow in the dog heart-lung preparation in which the coronary arteries were perfused by a pulsatile aortic pressure. The blood was conducted through a narrow glass tube inserted between the aorta and coronary arteries. The coronary flow was measured by photographing the movements of a mercury drop contained in the tube, a time lag of 0.02 seconds was present in their records. During systole, as aortic pressure rose, an initial increase in coronary flow was observed. Before the end of systole, coronary flow diminished and even stopped. During diastole, as the ventricle relaxed and aortic pressure fell, coronary arterial flow increased progressively. During the latter part of diastole, however, arterial flow sometimes diminished with a further fall in aortic pressure.

Thus, when the coronary arteries are perfused at a pulsatile pressure, two major forward movements of blood occur, one early in systole and one during diastole. This had been predicted in 1872 by Rebatel (105) who observed the flow in the right coronary artery of the horse. Anrep and his collaborators were careful to point out that the forward movement of blood at the mouth of the coronary arteries need not be accompanied by a simultaneous forward movement through the coronary capillaries. During the systolic rise in aortic pressure, the coronary arteries are dilated as a result of their inherent elasticity. In this way, the coronary arteries accommodate a large portion of the blood pumped into them during systole, so that measurement of blood flow at the mouth of the coronary

arteries over-estimates the blood flow through the coronary capillaries. During diastole, on the other hand, the elastic recoil of the coronary arteries propels the blood stored during systole. Intramural flow during diastole, therefore, is greater than that measured at the coronary orifice (5, 210).

The results of these studies of phasic variation in coronary blood flow have been confirmed in the intact dog by Machella and by Gregg and Green. Machella (140) measured coronary flow by inserting a hot wire directly into the anterior descending branch of the left coronary artery. As coronary flow changed, the temperature of the wire and therefore its resistance changed. Gregg and Green (86, 88) used an optically recording "orifice plate meter", described on page 4. They observed that in the left coronary artery, inflow diminished abruptly during isometric contraction and the direction of flow might actually momentarily reverse. The flow then accelerated during the rise of aortic pressure, reaching a peak during the middle of the rise. It then declined to a more or less constant rate of inflow during the latter part of systole. With the onset of isometric relaxation, coronary flow again increased, became maximal during mid-diastole, and then declined as the aortic pressure fell.

Mention should be made of another method of studying phasic variations in coronary flow used extensively by Wiggers, Gregg and Green (69, 89, 209). They argued that the changes in flow from moment to moment are due to differences in pressure between the central and peripheral ends of the coronary arteries. They therefore measured intramural flow by comparing the pressure at the central and distal ends of the arteries. This method assumed that a linear relationship exists between the difference in pressure and blood flow, and that the capacity of the vascular bed is unchanged during systole and diastole (78). Neither of these assumptions is correct. Gregg and Green (67, 88) have shown that a greater flow results from each millimeter of differential pressure during diastole than during systole. And, as was pointed out before, the capacity of the coronary vessels is greater during systole than during diastole because of the elasticity of the arteries. Technically difficult, the differential pressure method is not an adequate measure of coronary blood flow (93), yet its development was an important step in the study of cardiac physiology.

The flow through the *right coronary artery* is impeded by ventricular systole far less than through the left. The force of right ventricular contraction is much weaker than left. Therefore one would expect far less extravascular compression of the coronary vessels, and therefore less restriction of flow in the right compared with the left coronary artery (4). That this is actually the case was reported by Gregg (79) who used the technique of comparing central and peripheral coronary pressures. Gregg and Rotta (94) confirmed these experiments with the more accurate orifice plate meter. Coronary flow is restricted to only a slight degree by right ventricular systole. Right coronary arterial flow during systole is equal to or greater than that of an equivalent time interval of diastole, though total diastolic flow is greater than total systolic flow.

Variations in the outflow of the *coronary veins* during the cardiac cycle have not been studied extensively. Porter (117) reported that the principal blood

flow from an incised coronary vein was during systole. Langendorff (133) described the outflow from the coronary sinus of the isolated perfused cat heart. Blood flowed only during ventricular systole, and none during diastole or auricular systole. Langendorff believed that blood flowed from the coronary sinus as if it were squeezed from the heart by ventricular contraction. Anrep, Cruckshank, Downing and Rau (4) confirmed and extended these earlier observations. They measured phasic flow from the coronary sinus of a dog heart-lung preparation with a hot wire anemometer. A measurable outflow from the coronary sinus was present throughout the cardiac cycle. Three waves of increased flow were observed during systole. The first small wave occurred during auricular systole and was interpreted as due to auricular contraction, since it was not present in auricular fibrillation. The second small wave appeared during isometric ventricular contraction. The last large wave appeared at the beginning of ventricular ejection. Anrep and his associates interpreted this big increment of coronary flow as Porter and Langendorff had, ventricular systole compressed the coronary vessels and forced blood from the coronary sinus.

More recently Johnson and Wiggers (119) restudied the phasic variations in coronary sinus outflow. They reported in contradiction to Anrep that coronary sinus outflow occurred only during ventricular systole. The reason for the difference in results is not obvious, but the preparations were grossly different. Anrep used a dog heart-lung preparation in which coronary sinus outflow was led into a bottle and measured with a hot wire anemometer. Johnson and Wiggers studied the dog heart *in situ*, coronary sinus outflow was measured with a differential pressure manometer and the blood led through a tube directly into the superior vena cava.

To summarize, coronary arterial inflow is impeded at the end of systole by the resistance offered by the contracting ventricular muscle. The flow then increases during diastole as extravascular compression is removed, decreasing again during late diastole as aortic pressure falls. Coronary arterial inflow increases again during early systole as the aortic pressure rises. Since the contraction of the left ventricle is stronger than that of the right, the systolic decrease in coronary flow in the left ventricle is much greater than in the right, and if ventricular contraction is extraordinarily strong, left coronary arterial flow may actually cease at the end of systole. Actual measurements of flow through the coronary capillaries have not been made. Because of the elasticity of the coronary arteries, flow measured in the arteries is apparently greater during diastole than that through the coronary capillaries. Coronary sinus outflow is maximal during ventricular contraction and is sharply reduced or ceases during diastole.

*The Coronary Venous Return.* The blood which flows through the coronary capillaries can return to the ventricular cavities through three routes. The coronary capillaries join together to form a number of superficial venous trunks, the most prominent of which unite to form the coronary sinus which empties into the right auricle. Other veins join to form smaller superficial cardiac veins which empty into the right auricle. Still other capillaries communicate directly with

the ventricular cavities, particularly the right, through small *Thebesian veins* and sinusoidal vessels

The physiology of coronary venous return has been reviewed recently by Gregg, Shipley and Bidder (97). At first the coronary sinus was thought to drain the entire coronary blood flow (152). Later it was recognized that the coronary sinus drained only a portion of the flow. In general the major portion of left ventricular flow drains through the coronary sinus, whereas the major portion of right ventricular flow reaches the cardiac lumen through other channels. Anrep, Blalock and Hammouda (3) studied the distribution of coronary venous flow in the dog heart-lung preparation. Perfusing each coronary artery separately at a constant pressure, they measured coronary sinus outflow as each coronary artery was clamped in turn. Approximately two thirds of the blood flowing through the branches of the left coronary artery, but only one third of the blood flowing through the right coronary artery was collected by the coronary sinus. Katz, Jochim and Weinstein (123), studying coronary venous flow in the isolated, fibrillating dog heart reported much greater variation than Anrep and his collaborators in the proportion of blood from each artery drained by the coronary sinus. In different preparations, 12 to 70 per cent of left circumflex arterial flow and 25 to 65 per cent of the flow through the left anterior descending branch drained through the coronary sinus. None or at most 7 per cent of right coronary arterial flow drained through the coronary sinus. However, as Katz, Jochim and Weinstein pointed out, these data are not to be construed to indicate the proportions normally existing. In the fibrillating preparation intraventricular pressure is reduced to zero so that the normal systolic resistance to flow through accessory venous channels is absent.

Early studies seemed to indicate that coronary sinus outflow is a constant fraction of total coronary outflow. Evans and Starling (47) compared the outflow from the coronary sinus and from the pulmonary artery in an isolated dog heart perfused with blood at a constant pressure. The sole source of blood to the right auricle and ventricle was the coronary venous system. In this preparation the outflow from the pulmonary artery is the total coronary venous drainage except for the small amount draining directly into the left ventricle. The ratio of flow from the coronary sinus compared with total outflow was relatively constant at varying cardiac outputs, heart rates, and as later shown, aortic and coronary perfusion pressures (3). In these experiments, coronary sinus outflow was approximately 60 per cent of total coronary flow.

More recent data, however, indicate that under certain conditions the ratio between coronary sinus outflow and total outflow is not a constant, and therefore coronary sinus outflow cannot be used as a reliable index of total coronary venous flow (119, 121). Evidence for this has been reviewed by Moe and Visscher (150), and Jochim (117). The intraventricular pressure of a fibrillating heart is virtually zero. The coronary sinus outflow of such a fibrillating heart falls to a small fraction of the total coronary flow (121). Conversely, in a beating heart, when pulmonary arterial pressure and therefore right intraventricular pressure are elevated, the fraction of the total coronary outflow which

drains through the coronary sinus increases (119, 122) Studies by Moe and Visscher (148) have clarified this problem They observed that coronary sinus outflow was an accurate index of total coronary outflow when the aortic pressure perfusing the coronary arteries was more than 40 mm Hg higher than pulmonary arterial pressure, the relationship normally present However, when the difference between aortic and pulmonary arterial pressure was reduced to less than 40 mm. Hg, a relative increase in coronary sinus outflow occurred

The coronary venous blood which does not drain through the coronary sinus is returned to the cardiac lumen through several paths These include the smaller cardiac veins which enter the right auricle independent of the coronary sinus, and the small arterio-luminal vessels and Thebesian veins which connect the smaller coronary vessels with the ventricular lumens. These were demonstrated by Wearn (196, 197, 198) in perfused human hearts *post mortem* These extra sinus pathways are principally concerned with the venous return of the right ventricle The venous return to the left ventricular cavity through accessory vessels is not more than seven (151) or ten (123) per cent of the coronary blood flow

It has been assumed repeatedly that the major portion of the venous blood which does not drain through the coronary sinus entered the ventricles through Thebesian and arterio-luminal anastomoses The evidence for this was inferential, the usual procedure was to measure total coronary inflow and subtract from this coronary sinus outflow Recent experiments of Gregg, Shipley and Bidder (97) have shed new light upon this They measured the outflow from the anterior cardiac veins of the dog heart *in situ* either with a rotameter or directly with a graduate They observed that the major portion of the blood from the right coronary artery drains through the anterior cardiac veins into the right auricle, independent of the coronary sinus The larger of these anterior cardiac veins alone drain 50 to 92 per cent of the right coronary arterial flow These studies do not preclude venous drainage through the Thebesian vessels but imply that this is of lesser importance than had been thought previously

The question arises as to whether the cardiac muscle can be nourished through the Thebesian vessels or arterio-luminal sinusoids Early evidence seemed to support this view Pratt in 1898 (162) demonstrated that blood would flow from an incised coronary vein of the isolated cat heart when the sole source of blood was the right ventricular cavity Wiggers (208) introduced various drugs into the right ventricular lumen of a cat's heart perfused through its coronary arteries and observed effects on the left ventricle similar to those of intra arterially injected drugs

Apparently, however, under normal conditions no blood flows from the ventricular cavities into the coronary vessels Stella was unable to confirm Wiggers' experiments (181) and found that dye injected into the ventricular cavities after ligation of the coronary arteries did not penetrate the ventricular muscle appreciably (80) These experiments were confirmed by Eckstein, Roberts, Gregg and Wearn (36) They reported that when right intraventricular pressure was less than left, the normal relationship, India ink or Berlin Blue injected

into the right ventricular cavity did not penetrate more than a few coronary capillaries and sinusoids. On the other hand, when right intraventricular pressure rose above left, dye flowed from the right intraventricular cavity into the coronary vessels. That is, elevation of right above left intraventricular pressure reverses the pressure gradient between the coronary arteries and the right ventricular cavity, and blood will flow from the right ventricle into the coronary vessels. Thus, Katz, Jochim and Bohning (122) reported that increased intraventricular pressure in a cat heart-lung preparation perfused at a constant pressure through the coronary arteries increased coronary sinus outflow to 130 per cent of coronary arterial inflow. That is, when intraventricular pressure rose above the perfusing coronary pressure, blood flowed from the ventricular cavities through the cardiac muscle to the coronary sinus.

Under normal conditions, therefore, blood does not flow from the ventricular cavities into the coronary vessels. When right intraventricular pressure rises above coronary arterial pressure, retrograde flow from the ventricular cavities to the coronary vessels may occur. Since the blood in the right ventricular lumen is deficient in oxygen, it probably does not contribute materially to the nutrition of the cardiac muscle under these conditions.

To summarize, the coronary blood flow returns to the cardiac lumen through the coronary sinus, the superficial cardiac veins and Thebesian veins and sinusoidal vessels. The major portion of the blood flow through the left ventricle drains through the coronary sinus, and that of the right, through the anterior cardiac veins into the right auricle. The proportion of blood flow through each of these systems, however, varies considerably. Apparently under normal conditions only a small amount of blood reaches the cardiac lumen through the Thebesian veins and sinusoidal vessels. Retrograde flow from the right ventricular lumen into the coronary vessels can occur when right intraventricular pressure rises above coronary arterial pressure, but is probably of no importance since right ventricular blood is deficient in oxygen.

#### NERVOUS CONTROL OF THE CORONARY CIRCULATION

The blood vessels of the heart are richly supplied with nerve fibers. Woolard (214) showed that the larger arteries of the dog, cat, rabbit and guinea pig heart are supplied by both sympathetic and parasympathetic fibers in approximately equal proportions. However, the smaller vessels are innervated principally by the parasympathetic system. Wiggers (210) reviewed critically the mass of conflicting literature on coronary vasomotor control. Interpretation of many reported experiments is difficult because the techniques used were not definitive. Nervous stimulation produces a number of concomitant effects. The coronary flow may be altered directly by changing the caliber of the coronary vessels, or indirectly as the result of changes in the strength of ventricular contraction, cardiac rate and blood pressure. To differentiate direct from indirect effects, heart rate, the amplitude of cardiac contraction and blood pressure must be controlled. Conversely, studies on the isolated heart in which these factors are rigidly controlled may be misleading with regard to the effect of nervous stimulation in the intact animal.



An important obstacle to the study of vasomotor effects is the difficulty of separating anatomically sympathetic and parasympathetic fibers so that one may be stimulated or cut independent of the other. The anatomy of these autonomic fibers was studied extensively in the dog by Greene (72). The parasympathetic fibers to the heart are carried in the cervical vagus nerves. The sympathetic fibers arise in the upper thoracic spinal cord, traverse the upper thoracic ganglia, and synapse with post-ganglionic fibers in the superior, and middle cervical ganglia and particularly in the stellate ganglia, the fusion of the inferior cervical and first thoracic ganglia. Post-ganglionic fibers then travel to the heart via the superior, middle and inferior cardiac nerves. In addition, there are post-ganglionic sympathetic fibers from the first four to six thoracic ganglia which go directly to the heart (72, 206). Post-ganglionic sympathetic fibers are also present in the lower cervical vagus nerves. Before they reach the heart, the cardiac nerves form a plexus in which differentiation of the various nerve fibers is all but impossible. Further, in the dog the vagus and sympathetic nerves travel in the same sheath. Greene pointed out that at best only a few millimeters of cervical vagus just below the ganglion nodosum are free of sympathetic nerve fibers, and a few millimeters of sympathetic nerve below the superior cervical ganglion are free of vagal fibers. Nervous connections between the two ganglia may exist. The close anatomic association of sympathetic and parasympathetic fibers makes it most difficult to determine the effects of sympathetic and parasympathetic stimulation, a fact frequently overlooked.

Finally, variations in the effect of nervous stimulation among various species of experimental animal and among individuals of the same species must be stressed. Thus, Greene (72) reported that among dogs, young animals seemed more reactive than older animals, particularly to constrictor impulses. Therefore care must be exercised in transposing the results of animal experiments to human physiology.

*Action of Neurohumors* To circumvent anatomic difficulties in separating sympathetic and parasympathetic nerves, the action of the respective neurohumors has been studied extensively. However, their use introduces new difficulties. For example, *acetylcholine* is believed to be parasympathomimetic, yet in at least one location, the sweat glands, acetylcholine is apparently the sympathetic neurohumor (29). And *adrenalin*, the sympathomimetic secretion of the adrenal medulla, is not identical in action with *sympathin*, the humoral mediator of the sympathetic nervous system (26). Adrenalin has both vasoconstrictor and vasodilator properties. Apparently two varieties of sympathin exist, one vasodilator and the other vasoconstrictor. Therefore the effect of adrenalin on coronary arteries is not necessarily identical with that of sympathetic nervous stimulation.

The action of *acetylcholine* on the coronary blood flow of the isolated fibrillating heart perfused at a constant pressure was studied by Katz and his collaborators (126). An increase or decrease of pulmonary arterial outflow was interpreted as due to vasodilation or constriction respectively. With this technique, acetylcholine produced dilation of the coronary vessels of the dog. In

concentrations above 1:820,000 it caused vasoconstriction in the cat, but in more dilute solutions, either vasoconstriction or dilation. All these effects were diminished or abolished by atropine, which inhibits parasympathetic nervous impulses. Acetyl-beta-methylcholine (*mecholyl*), a derivative of acetylcholine with a more prolonged action, caused vasodilation in the dog and vasoconstriction or no response in the cat. Wedd (201, 202) reported that acetylcholine and carbaminoylcholine (*doryl*) first increased and then decreased coronary sinus outflow in isolated cat, dog and rabbit hearts. Acetylcholine increased coronary blood flow in the dog heart-lung preparation (2, 155). Injection of *mecholyl* into the unanesthetized, trained dog was followed by an increase in coronary arterial flow as measured by thermostromuhr (46).

In general, then, acetylcholine increases coronary blood flow in the dog. Its action in the cat and rabbit is not clear.

The action of *adrenalin* on coronary blood flow has been investigated more extensively. It varies from species to species, among individuals of the same species, and even along different portions of the same coronary artery. To determine the vasomotor action of *adrenalin*, secondary effects due to changes in heart rate, coronary blood pressure, and peripheral resistance must be carefully excluded. Further, as Markwalder and Starling (142) pointed out and Gregg and Shipley (11) recently reemphasized, *adrenalin* increases the metabolic rate of tissues and the resultant metabolites may themselves affect the caliber of the blood vessels.

Studies of the effects of *adrenalin* upon isolated coronary arterial rings are in general unsatisfactory. Rigid control of temperature is important since changes in temperature alter the caliber of the coronary arteries (27, 28). The coronary arterial segments which can be studied are necessarily of large or moderate diameter. The smallest arteries and arterioles which exert the most influence on peripheral resistance to flow cannot be studied in this manner. *Adrenalin* apparently dilates the isolated coronary arteries of the calf, sheep, pig (11, 27) and dog (28). In general, the larger coronary arteries of human hearts *post mortem* are constricted by *adrenalin*, (11) but the smaller, more distal branches are dilated (28). However, the same strip of human coronary artery may be dilated by large and constricted by small doses of *adrenalin* (129). When constrictor effects were abolished by ergotoxin, *adrenalin* dilated both dog and human coronary arteries (28, 129). That is, isolated strips of coronary artery are usually dilated by *adrenalin*. In those human arterial segments in which *adrenalin* causes vasoconstriction, vasodilation occurs when the constrictor effect is abolished by ergotoxin. Since the smallest vessels cannot be studied by this technique, conclusions cannot be drawn from these experiments regarding the action of *adrenalin* on coronary blood flow.

The effect of *adrenalin* on hearts arrested either by chemical changes in the perfusate (102, 106, 130, 207) or by cardiac failure (12) is variable, and since the technique is unphysiologic, without significance. Studies on the isolated fibrillating heart are more informative. In this preparation the effect of a drug upon coronary flow may be studied independent of changes in cardiac rate, coronary arterial pressure and peripheral resistance, changes in coronary flow

is presumably due to changes in the caliber of the coronary vessels. Hamouda and Kinosita (106) observed that adrenalin increased coronary flow in the isolated fibrillating rabbit heart. Katz and his associates reported that the administration of adrenalin to the fibrillating cat heart was followed either by vasoconstriction or vasodilation. In the dog heart, vasodilation resulted, either alone or preceded by transient vasoconstriction. Therefore the action of adrenalin on the blood vessels of the fibrillating heart is variable.

Although studies on the fibrillating heart may be useful to determine the effect of drugs on the caliber of the coronary vessels, they do not furnish information concerning the response of the beating heart. Adrenalin increases heart rate, the strength of cardiac contraction, and aortic and coronary arterial pressures. Further, if the vagi are intact, the increased cardiac output will increase coronary blood flow reflexly (9).

The effect of adrenalin on the isolated beating perfused heart depends upon the species studied and the dosage used. The coronary blood flow of the rabbit is decreased by low (106) and increased by high (12, 106) concentrations of adrenalin. The decrease in flow with small doses may be due to increased extravascular resistance because of the increased vigor of ventricular contraction (106). The coronary blood flow of the isolated beating monkey heart is decreased by adrenalin (12), and that of the human heart revived *post mortem* is first increased and shortly thereafter decreased (130).

In the anesthetized dog, the coronary arterial flow of the innervated heart *in situ* is increased by administration of adrenalin. In the first experiments reported (77, 152, 153) the technique of measuring coronary flow was not reliable. However, using the more accurate thermostromuhr method, Wégria, Essex and their associates (46, 205) observed an increase in flow through both right and left coronary arteries in the anesthetized dog and the unanesthetized trained dog as well.

In summary, then, adrenalin increases coronary flow in the intact, innervated dog heart. Studies on isolated coronary vessels and the fibrillating heart indicate that the coronary arteries of most species are dilated by adrenalin. However, adrenalin may constrict the larger human coronary arteries and sometimes those of the cat. In the intact heart, however, the increased coronary arterial pressure more than compensates for any increase in peripheral resistance, whether due to vasoconstriction or increased extravascular compression. Since its action and that of sympathetic nervous stimulation need not be identical, care should be exercised in drawing conclusions from experiments with adrenalin.

**Vagal Stimulation.** In 1896 Porter (161) studied the effect on coronary blood flow of stimulation of the cardiac end of the cut vagus nerve of the isolated cat heart. He reported that a stimulus not strong enough to change heart rate decreased coronary outflow from the incised right ventricle. The same result was observed in a non beating heart. Porter therefore believed that vagal stimulation caused vasoconstriction in the cat heart. Since vasoconstriction was followed by vasodilation in one experiment, Porter concluded that the vagi might carry both vasoconstrictor and vasodilator fibers.

Anrep and Segall (9) obtained similar results in the dog heart-lung preparation.

measuring coronary sinus outflow. Bilateral vagal section increased coronary flow even though heart rate remained constant. Stimulation of the peripheral end of the cut vagus nerve at first diminished and then increased coronary flow above normal. Blood pressure was maintained constant in these experiments and the bradycardia which accompanied vagal stimulation was not sufficient to affect coronary flow. Therefore, like Porter, Anrep and Segall believed that the vagi carry vasoconstrictor impulses. They attributed the delayed dilator effects to the presence of post-ganglionic sympathetic nerve fibers in the lower cervical portion of the dog vagus nerve. These dilator effects usually did not appear if the vagus was stimulated high in the neck where sympathetic fibers ordinarily have not yet joined the vagus (72).

Apparently, in the isolated human heart revived *post mortem* the vagi constrict the coronary vessels. Kountz, Pearson and Koenig (130) observed that coronary inflow was decreased by vagal stimulation in hearts in which the ventricular rate was constant because of complete auriculo-ventricular dissociation.

The effect of parasympathetic stimulation upon the vigor of cardiac contraction was not controlled in any of these experiments. Katz and Jochim (120) stimulated the vagi to the isolated dog heart in which the nerves were preserved. The brain and coronary arteries were perfused simultaneously at a constant pressure, and the heart was set into fibrillation so that coronary flow would be unaffected by changes in the force of ventricular contraction. The outflow of the pulmonary artery was used as a measure of coronary flow. In contrast to experiments reported by others, section of both vagi in the neck decreased coronary flow, and stimulation of the peripheral end of the cut vagi either increased flow or was without effect. Katz and Jochim therefore concluded that the vagi carried vasodilator rather than vasoconstrictor impulses to the heart.

None of these studies defines the action of the vagus in the intact animal. Rein (167) measured coronary blood flow in the intact dog with a thermostromuhr. Section of the vagi increased, and stimulation decreased coronary blood flow. He stimulated the vagi high in the neck, where interference from accompanying sympathetic fibers is minimal. These results were confirmed by Essex and his collaborators (43) with an improved thermostromuhr. They also observed an increase in blood flow after injection of atropine which blocks the transmission of parasympathetic impulses (44).

Evidence concerning the effect of vagal stimulation on the caliber of the coronary vessels is therefore conflicting. In the beating heart the vagus seems to be predominantly vasoconstrictor. In the fibrillating heart, in which the effect of nervous stimulation on muscular contraction is minimized, the vagus, as elsewhere in the body, apparently dilated the coronary vessels. However, in the intact animal, stimulation of the vagi decreases coronary flow.

*Sympathetic Stimulation.* Similarly the effects of sympathetic nervous stimulation on the coronary circulation have not been defined clearly. Most studies on the isolated heart have been unsatisfactory because the methods used to measure blood flow were inaccurate, because of confusion between the sympathetic and parasympathetic nerves, and because heart rate, blood pressure and the vigor of cardiac contraction were not controlled (172). Further, unless the

vagi are sectioned, coronary flow may increase reflexly when the sympathetic nerves are stimulated as the result of the increase in cardiac output (9)

Kountz, Pearson and Koenig (130) measured coronary arterial inflow in the strongly beating human heart revived *post mortem*. When the ventricular rate was constant because of auriculo-ventricular block, stimulation of the sympathetic nerves to the heart increased coronary blood flow. Sympathetic nervous stimulation also increased the arterial inflow (107) and coronary sinus outflow (30) of the dog heart-lung preparation.

However, the effect of sympathetic stimulation is not clear when changes in the vigor of cardiac contraction are minimized by the use of the isolated fibrillating heart. Katz and Jochim (120) measured pulmonary arterial outflow in the fibrillating dog heart in which the head and coronary arteries were perfused at a constant pressure. Stimulation of the stellate ganglia after the vagi had been cut resulted in coronary vasodilation in 7 experiments, vasoconstriction in 5 experiments, and either a biphasic or doubtful change in 27 experiments. These studies suggest that the sympathetic nerves include both vasoconstrictor and vasodilator fibers.

In the intact animal, stimulation of the sympathetic nerves increases coronary blood flow. Morawitz and Zahn (153) reported that sympathetic nervous stimulation increased coronary sinus outflow of dogs and cats, heart rate, the amplitude of cardiac contraction and blood pressure were not controlled. Greene (71, 72) also noted an increase in coronary sinus outflow upon sympathetic nervous stimulation in the intact dog. This was true when the stellate ganglia were stimulated after they had been separated from the spinal cord by sectioning the thoracic pre-ganglionic rami to minimize reflex effects. Coronary sinus outflow was also increased upon stimulation of the post-ganglionic fibers of the 5th and 6th left thoracic ganglia which go directly to the heart. Greene observed that the lower cervical vagal trunk might contain vasodilator fibers which he believed were sympathetic in origin. Unfortunately, however, coronary sinus outflow is not an accurate index of coronary blood flow.

The effect of sympathetic nervous stimulation upon coronary blood flow in the intact animal was re-examined by Gregg and Shipley (96). They recorded the minute volume of coronary arterial inflow with a rotameter, and phasic variation in flow with an orifice plate meter. In the intact dog stimulation of the stellate ganglion usually increased flow into the main branch of the left coronary artery, though in some experiments the increase was slight. The increase occurred even though blood pressure and heart rate were maintained constant. Studies with the orifice meter indicated that diastolic blood flow was increased and systolic flow decreased. Similar changes were observed in the right coronary artery. Therefore Gregg and Shipley believed that the increased flow upon stellate ganglion stimulation is at least partly the result of coronary vasodilation. They pointed out that this might be a direct action of sympathetic nervous stimulation upon coronary vessels, or the effect of an accumulation of metabolites as the result of increased cardiac metabolism (95). The increased coronary flow might also be due to reflex inhibition of vagal impulses secondary to the increase in cardiac output (9).

To summarize, the effect of sympathetic nervous stimulation upon the isolated fibrillating heart varies among species and among individuals of a species. However, in the isolated, beating heart, the heart-lung preparation and the intact animal, sympathetic nervous stimulation increases coronary blood flow. This is probably due at least in part to coronary vasodilation.

*Reflex Control of Coronary Blood Flow Reflexes of Cardiac Origin* In the denervated heart-lung preparation, coronary blood flow does not change with cardiac output, as long as other factors, notably arterial blood pressure are constant (142). However, if the nerves to the heart are intact, coronary blood flow will increase as cardiac output increases. Anrep and Segall (9) observed this in the innervated dog heart-lung-brain preparation. The brain was supplied with oxygenated blood through the brachio-cephalic artery by means of an artificial pump. Coronary sinus outflow was extremely sensitive to changes in cardiac output. In some experiments, trebling cardiac output doubled coronary sinus outflow, although aortic and coronary arterial pressures were constant. The slight change in cardiac rate which resulted from the Bainbridge reflex was not sufficient to account for the increased coronary sinus outflow. Anrep and Segall also noted that in the innervated heart-lung preparation the same rise of blood pressure caused a much greater increase in coronary sinus outflow when the cardiac output was large than when it was small.

This increase in coronary blood flow when cardiac output is increased was observed in the dog heart *in situ* by Green and Gregg (68, 87) whether the coronary arteries were perfused at a constant pressure or with the normal pulsatile aortic flow. In the former instance coronary arterial inflow was measured with a constant pressure flow meter, and in the latter, with an orifice plate meter. The cardiac output was increased by infusing blood into the jugular vein. When the coronary arteries were perfused with the pulsatile aortic outflow, some of the increased cardiac output was apparently due to the increase in systolic blood pressure which resulted from the increased cardiac output. Most of the increased coronary flow, however, was during diastole and was probably the result of reflex inhibition of vagal coronary vasoconstriction. However, the effect of vagotomy was not studied.

The vagus nerves to the heart are in a state of continual, tonic activity regulating the caliber of the coronary blood vessels. In the dog, sympathetic tonic activity is more difficult to demonstrate. Anrep and Segall (9) observed that the coronary sinus outflow of the dog heart-lung-brain preparation increased when the vagi were sectioned. This preparation, in which the sympathetic nerves were intact, now behaved as if totally denervated, for an increase in cardiac output failed to increase coronary sinus outflow. Anrep and Segall thought this meant that in the innervated preparation, the increase in coronary flow when cardiac output increased was mediated reflexly through the vagus nerve. They believed that the acceleration of blood flow after vagal section indicated the presence normally of a "parasympathetic tone" in which parasympathetic stimuli held the coronary vessels in a continual state of partial constriction.

Tonic control of coronary blood flow by the vagus nerve has also been demonstrated in the intact dog. Essex and his associates (43) observed the coronary arterial flow of the trained, unanesthetized dog was doubled by cutting the vagi. Changes in coronary flow with exercise were then the same in both vagotomized and totally denervated dogs. The increase in coronary arterial flow when cardiac output increased was abolished by vagotomy (43, 167) and by the administration of atropine, which blocks the transmission of vagal impulses (58).

Evidence for the presence of tonic sympathetic control of coronary blood flow is meager. Essex and his associates (43) noted that the coronary flow of sympathectomized dogs increased with exercise in the same way as that of the normally innervated animal. Katz and Jochim (120) sectioned the stellate ganglion to the isolated fibrillating dog heart after the vagi had been cut. When a change in coronary blood flow occurred after this procedure, it was an increase, but this was not prominent. In the intact dog, on the other hand, Gilbert and his associates (57) found some evidence for sympathetic dilator tone. The decrease in coronary flow measured with the thermostromuhr or Morawitz cannula which occurred when the decerebrate dog's nasal mucosa was irritated with ice water was not abolished by section of the vagi or injection of atropine. These experiments are suggestive but not definitive.

The evidence therefore implies that in the dog the vagus nerves to the heart are in a state of continual tonic activity regulating coronary blood flow. Sympathetic tonic activity is much less prominent. This corresponds with the fact that anatomic studies show that the nerves to the smaller vessels are predominantly parasympathetic. These experiments in no way elucidate the degree of tonic sympathetic and parasympathetic control in man.

*Reflexes of Extra-Cardiac Origin.* The changes in coronary blood flow which result from extra-cardiac stimuli are of great clinical interest and may help to elucidate the relationship between angina pectoris and such incitants as eating, abdominal distention, cold and exercise. Stimulation of many afferent nerves will increase coronary blood flow. However, this does not tell the whole story, for these stimuli may also increase the work of the heart or decrease coronary arterial blood pressure. Whether symptoms of coronary insufficiency will occur depends upon the balance between the needs of the heart and the coronary blood flow.

Greene (73) investigated the effect of stimulating various afferent nerves upon coronary sinus outflow in the intact dog. As a general rule, weak stimulation of afferent nerves increased coronary sinus outflow, while stronger stimulation decreased flow and frequently blood pressure as well. As has been emphasized, coronary sinus outflow is not an accurate index of total coronary blood flow. The increase in coronary sinus outflow was observed upon stimulation of the central end of the cut sciatic nerve, the phrenic nerves, the celiac ganglion, the nerves to the celiac ganglion from the region of the gall bladder and common duct, and the right splanchnic nerve (114). Stimulation of the central end of the branches of the vagus from the stomach and hepatic regions gave inconsistent results, sometimes increasing coronary sinus outflow (73, 114).

*Digestion* of a mixed meal increased coronary arterial inflow in the quietly resting dog (40). *Distention* of the esophagus, stomach, and gall bladder of the dog were reported by Hinrichsen and Ivy (114) to increase coronary sinus outflow. Gilbert, LeRoy and Fenn (58) repeating the studies of Von Bergmann (194) observed that coronary arterial inflow, a more accurate measure of flow, was usually decreased by distention of the stomach or peritoneal cavity. Occasionally coronary flow either increased or was unchanged. The decrease in flow occurred despite little or no change in blood pressure, and was prevented by atropine, indicating that the reduction was mediated through parasympathetic nerves. Distention of the gall bladder or distention or irritation of its ducts also decreased coronary flow through parasympathetic reflexes (54).

An increase in *cerebral blood pressure* slightly diminished, and a fall in cerebral blood pressure increased coronary sinus outflow in the dog heart-lung-brain preparation (9). Stella (182), Hochrein and Keller (115), and Wégria, Essex, and Herrick (204) demonstrated that these changes were mediated through the carotid sinus. A reduction in *carotid* sinus pressure increased coronary arterial inflow. Stimulation of the *aortic nerve* elicited either reflex constriction or dilation of the coronary vessels depending upon the frequency and strength of current used.

Changes in coronary blood flow with *exercise* are controlled largely through nervous reflexes. Greene (76) demonstrated that spontaneous skeletal movements of dogs lightly anesthetized with ether were accompanied by an increase in coronary sinus outflow, independent of changes in blood pressure and heart rate, and presumably of reflex origin. Essex, Herrick, Baldes and Mann (42) studied the effect of exercising on a treadmill on coronary arterial inflow in trained, unanesthetized dogs. Blood flow was measured with a direct current thermomicrostromuhr placed around the artery four or five days before. They observed that coronary flow increased rapidly at the beginning of exercise and with each increment of work. The coronary flow frequently declined somewhat from its maximum after exercise had continued for a short time. This was also true to a lesser extent after each new increment. With the cessation of work, coronary blood flow returned to normal in one or several minutes. Coronary blood flow was increased by exercise as much as 400 per cent above the resting level. The increase roughly paralleled the increase in heart rate, but not blood pressure, for at low rates of work the increased flow was not accompanied by a sustained rise in blood pressure. Therefore the increase in coronary blood flow with exercise could not be attributed to an increase in aortic blood pressure alone. Sympathectomized dogs were found to behave in a manner indistinguishable from normal animals, coronary blood flow increasing with exercise (43). On the other hand, 30 days after bilateral vagotomy coronary blood flow increased with exercise only if arterial blood pressure increased. Total denervation of the heart was followed immediately by an increase of as much as 100 per cent in coronary blood flow. Subsequent to this, exercise caused a tachycardia of only about 10 beats per minute. In the totally denervated dog, as in the vagotomized dog, coronary blood flow was dependent principally on blood pressure.

Exercise, then, increases coronary blood flow both by increasing arterial blood pressure and by coronary vasodilation. The vasodilation is apparently mediated



through the vagus nerve, and disappears after vagotomy or total denervation. Such small changes in coronary flow unexplained by changes in blood pressure or changes in vagal tone may be due to the increase in body temperature accompanying exercise, or to an increase in circulating metabolites.

*Cutaneous pain* increases coronary blood flow (73, 115). The concomitant increase in blood pressure which may occur, however, may disproportionately increase the work of the heart and relative coronary insufficiency may result. *Cooling the skin*, which will induce anginal attacks in human patients (53) also increases coronary arterial flow in the dog (160), an effect abolished by section of the vagus nerve. Cooling the mucous membrane of a decerebrate dog with ice water, however, decreases coronary flow. This occurs despite vagal section or the administration of atropine and may be due to inhibition of sympathetic tonus (57).

Thus various stimuli—exercise, pain, cooling of the skin—which may induce anginal attacks may be associated in the experimental animal with an increase in coronary blood flow. However, all these stimuli may concomitantly increase arterial blood pressure and the work of the heart. In addition, one may surmise that the presence of arteriosclerosis will limit the degree to which coronary blood flow may be increased. If cardiac work increases disproportionately to the increase in coronary blood supply, relative coronary insufficiency and anginal pain will result.

#### PHARMACOLOGY OF THE CORONARY CIRCULATION

Studies of the pharmacology of the coronary circulation have helped to explain the clinical efficacy of certain drugs used in the treatment of coronary arterial disease. The pertinent literature has been reviewed by Smith (176) and more recently by Essex (39), Jochim (117), and Green (66). The effect of drugs may be studied in the intact animal. Equally important, the mechanism by which this effect is achieved must be determined. A drug may act directly on the coronary vessels, or indirectly by altering coronary blood pressure, the peripheral resistance which the cardiac muscle offers to flow, or the metabolism or cardiac muscle. In most reported experiments, particularly those on isolated heart or heart-lung preparations, the dosages of drugs employed have been far in excess of those used clinically. Since the action of a drug frequently differs in low and high concentrations, erroneous conclusions may be drawn too readily from the results of animal experiments. In addition, there are species and individual variations in response. And, as Kountz and Smith (131) have shown, the normal and the failing heart may respond differently to the same drug.

*Nitrites* The nitrites have been used widely in the treatment of angina pectoris. They increase the volume of coronary blood flow and relieve the relative myocardial ischemia with its accompanying pain. Apparently this is achieved by dilation of the coronary vessels despite a concomitant fall in arterial blood pressure.

Sodium nitrite has been reported to increase coronary blood flow in the isolated, revived, normal human heart (129, 130) and heart-lung preparation (2, 21) and in the dog heart *in situ* (175). In the anesthetized dog, flow increased both

in systole and diastole, presumably because of vasodilation (23). Isolated strips of ox, pig (193) and human (129) coronary arteries were dilated by sodium nitrite. Introduced into the fluid perfusing the isolated, fibrillating dog heart, it increased coronary flow as measured by pulmonary arterial outflow (126). Since perfusion pressure was constant and extra-vascular peripheral resistance virtually *nil*, the increased outflow was interpreted as evidence of coronary vasodilation.

Sodium nitrite therefore increased coronary blood flow in human and animal hearts, principally by dilating the coronary vessels and in spite of a fall in arterial blood pressure. However, in the failing heart, coronary arterial flow may decrease. This was demonstrated in the dog heart *in situ* by Smith, (175) and later by Kountz and Smith (131) in the isolated revived dilated human heart.

*Amyl nitrite*, inhaled by the anesthetized or unanesthetized dog, increased coronary arterial blood flow as measured with the thermostromuhr (40, 205). In the unanesthetized dog the nasal passages were first cocaineized to eliminate reflex effects due to local irritation by the drug. The unanesthetized dog was relatively refractory to a second dose of amyl nitrite administered immediately after the first. Amyl nitrite increased coronary flow in the isolated monkey heart (12) and dog heart-lung preparation (21) and dilated isolated ox and pig coronary arterial strips (193).

*Nitroglycerine* also increased coronary arterial blood flow when administered intravenously or by mouth to the unanesthetized dog (40, 46), or intravenously to the anesthetized dog (205). Studies on isolated coronary arterial rings (193), the isolated fibrillating dog heart (126) and anesthetized intact dog (23) indicate that the increased flow is due at least partly to vasodilation. Smith (175) studied the effect of nitroglycerine on myocardial ischemia in the dog. Transient relief of cyanosis was observed in the muscle distal to the ligation of a small branch of the left coronary artery. He believed this was because the collateral arterioles and capillaries of the effected area were dilated.

*Digitalis and its Derivatives*. The use of digitalis and allied compounds in the treatment of coronary arterial disease has been the subject of much debate. Those who disapprove base their argument partly upon reports that these drugs constrict coronary vessels. Actually, experimental evidence of vasoconstriction by therapeutic doses is unconvincing. Nor is there adequate clinical evidence of vasoconstriction. Thus, Gold and his associates (61) reported that the administration of digitalis to 120 selected patients did not affect the course of angina pectoris. When clinical indications exist, digitalization should not be withheld because of fear of coronary vasoconstriction.

Studies of the action of digitalis upon the coronary vessels of laboratory animals have been inconclusive. Not enough attention has been paid to changes in cardiac rhythm, vagal tone, and the strength of myocardial contraction, all of which influence coronary flow in the intact animal. Further, in most experiments, relatively large, toxic doses have been used. Nowhere are the difficulties of transposing experimental results to the bedside better illustrated than in studies of digitalis.

In the intact, anesthetized (160) and unanesthetized (32, 41, 45) dog, repeated studies indicate that in doses comparable to those used therapeutically, *digitalis*, *strophanthin*, *digilanids A, B and C* and *digitoxin* are without effect on coronary arterial flow as measured with the thermostromuhr. Toxic doses of *digitalis*, *digitoxin* or *strophanthin*, however, decrease coronary flow. When coronary sinus outflow was measured, the results were not as clear cut. Sakai and Saneyoshi (171) observed that *strophanthin* in therapeutic doses did not alter coronary flow in the cat. Others observed that *ouabain* and *strophanthin* usually decreased coronary flow (56, 59) but the effect of *digitalis* leaf and *digitoxin* varied. However, in some experiments the concentration of drugs was sufficient to alter blood pressure, an effect not found with non toxic doses.

The effect of *digitalis* and related compounds upon the coronary vessels of various isolated preparations is less well understood. Kountz and Smith (131) studied the action of *digitalis* upon coronary arterial inflow in isolated, beating human hearts revived *post mortem*. *Digitalis* increased coronary flow if the heart was dilated, but decreased flow if the heart was of normal size. These experiments imply that *digitalis* may increase the coronary flow of the failing heart.

*Digitalis*, *strophanthin*, and the *digitalis* glycosides are said to constrict isolated strips of coronary arteries (38, 104, 103), though dilation has been reported as well (27, 193). *Digitoxin* decreased coronary flow in the isolated, perfused, beating heart (138), but *strophanthin* did not affect coronary flow except in doses causing cardiac arrest (104, 106, 108). Variable results have also been reported for the effect of *digitalis* and its derivatives on coronary sinus outflow in the heart-lung preparation (21). Ginsberg, Stoland and Siler (59) noted a biphasic effect, a temporary decrease in coronary sinus outflow being followed by an increase. However, coronary sinus outflow is not a reliable index of coronary flow.

K *strophanthin*, *digifolin* and *ouabain* were reported by Lindner and Katz (67) to have a variable effect upon coronary flow in the isolated, perfused, fibrillating dog heart, so that these drugs seemed at one time to be vasoconstrictor and at another, vasodilator. What effect the drugs had upon the character of ventricular fibrillation and thus upon peripheral resistance to flow was not described.

To summarize, the action of *digitalis* and allied compounds upon various isolated preparations is not clear. In the isolated human heart, coronary arterial flow was increased by *digitalis* if the heart was dilated, decreased if the heart was normal in size. In the intact dog, *digitalis* and its derivatives were without effect on coronary arterial inflow in doses comparable to those used clinically, although toxic doses decreased arterial flow. These experiments imply that the presence of coronary arterial disease does not contraindicate the use of *digitalis*.

**Xanthines** The xanthines are used extensively in the treatment of coronary arterial disease. Both in the isolated heart and in the intact animal, parenterally administered xanthine derivatives increase coronary flow. Of course, this does not mean that the same drugs are therapeutically effective by mouth. Recent experiments (82, 211) have not borne out the earlier hope that the xanthines might induce a collateral circulation which would diminish the size of a myo-

cardial infarct after coronary occlusion (52) Nor is there adequate evidence that the xanthines improve an impaired human coronary circulation (22) As Gold (60) has emphasized, this does not preclude the use of the xanthines in coronary arterial disease as diuretics or for the relief of concomitant respiratory distress

The coronary vasodilator properties of the xanthines were reviewed by Fowler, Hurevitz and Smith (52) and more recently by Boyer (22) Apparently, *theophylline* alone or with ethylene diamine (*aminophylline*) is the most potent xanthine vasodilator, *theobromine* and *caffeine* are less effective (108) Rather large doses of aminophylline increased coronary arterial flow in anesthetized (205) and unanesthetized (46) dogs The increased flow induced by aminophylline or *theamine* (theophylline mono-ethanolamine) was principally during diastole, and was sometimes preceded by decreased flow during systole (23) The decreased systolic flow was attributed to an increased vigor of ventricular contraction which increased extravascular compression of the coronary vessels Total coronary flow increased despite a fall in blood pressure, implying that vasodilation occurred Whether this increased flow was sufficient to meet the simultaneously increased needs of the heart muscle was not clear

Theophylline and aminophylline were reported to increase coronary flow in the isolated, fibrillating dog heart (137) and isolated, beating cat (103) and rabbit (108, 178) heart Theophylline and aminophylline also increased coronary arterial inflow in the revived human perfused heart or heart-lung preparation whether the heart was normal in size or dilated (131)

*Theobromine*, *theobromine sodium salicylate* and *caffeine* are not as consistent coronary vasodilators as theophylline and aminophylline (178) They increased coronary arterial inflow in normal human hearts revived post mortem (2, 129, 131) and, except for theobromine, in dilated human hearts as well Gilbert and Fenn (55) believed theobromine and its salts increased coronary sinus outflow in the intact anesthetized dog more than theophylline, aminophylline or caffeine, theobromine sodium acetate decreased the mortality rate of dogs during the first 24 hours after coronary arterial ligation from 70 to 23 per cent (134) Unfortunately the ultimate fate of the dogs in this study was not described Large doses of caffeine increased coronary flow in the perfused isolated, fibrillating dog heart (137) and the beating cat (103) and rabbit heart (108)

*Quinidine* Quinidine is an alkaloid widely used in the treatment of irregularities of cardiac rhythm It is without effect on coronary flow in the isolated, revived, perfused human heart (129) and dog heart-lung preparation (21) and isolated fibrillating heart (37) Nor does quinidine dilate human coronary arterial segments post mortem (129)

*Opiates* Although morphine and its derivative are probably the drugs most frequently employed in the therapy of myocardial infarction, few studies have been made of their effects on the coronary circulation Apparently *morphine* dilates the coronary vessels of isolated dog (37) and human hearts (129) to some degree *Papaverine* is a much more active coronary vasodilator and in doses comparable to those used clinically increased coronary arterial flow of unanes-

thetized, trained dogs (46) Papaverine also increased coronary flow in the anesthetized and unanesthetized dog (205) and the revived, isolated, perfused human heart (129) and heart-lung preparations (2) However, its clinical use in angina pectoris is often disappointing (60, 64)

*Posterior Pituitary Substances* *Pituitrin*, which contains both oxytocic and pressor principles of the posterior pituitary gland, and *pitressin*, which is primarily pressor principle, cause prolonged and intense coronary vasoconstriction This has been demonstrated repeatedly in the anesthetized (205) and unanesthetized (46) intact dog, the dog heart lung preparation (21, 113, 155), the perfused, isolated, fibrillating dog heart (126) and the isolated, perfused, rabbit heart (101) Pituitrin decreased coronary flow in the revived, normal, isolated human heart (129) and heart-lung preparation (2, 130) However, in the dilated heart, coronary arterial flow increased (131) Because of its prolonged vasoconstrictor effects, pituitrin should be used with circumspection in the presence of coronary arterial disease

*Sympathomimetic Drugs* The action of *adrenalin* has been discussed in the section on Nervous Control of the Coronary Circulation *Ephedrine* is apparently a coronary vasodilator, increasing coronary sinus outflow in the intact dog (184) and in the dog heart-lung preparation (155) more than would be predicted from the concomitant rise in blood pressure.

*Paredrine*, an adrenalin derivative with primarily pressor action, caused prompt and prolonged coronary dilation of considerable magnitude in the perfused, isolated, fibrillating dog heart (37) The net effect in the intact animal cannot be predicted from these experiments. Coronary vasodilation and the rise in aortic blood pressure increase coronary blood flow, but concomitantly the strength of ventricular contraction increases, and with it, systolic resistance to coronary flow

*Parasympathomimetic Drugs* *Acetylcholine* and *mecholyl* (acetyl beta-methylcholine) have been discussed in the section on Nervous Control of the Coronary Circulation The alkaloid *pilocarpine* was reported to increase coronary blood flow in the isolated, revived, human heart, at the same time decreasing heart rate It was without effect on isolated rings of human coronary arteries (129, 130)

*Miscellaneous Drugs* *Atropine*, which blocks parasympathetic nervous stimuli, increased the coronary arterial blood flow of anesthetized (205) and unanesthetized (46) dogs This was invariably accompanied by an increase in pulse rate Atropine also increased coronary sinus outflow in the dog heart-lung preparation (9) The effect of atropine on the human coronary circulation is not clear Kountz (129, 130) observed that atropine increased the heart rate and diminished the coronary flow of the revived, isolated, perfused human heart It was without effect on isolated coronary arterial rings

*Coramine* or *nikethamide* (piperidine betacarboxic acid diethylamide) in doses relatively large compared with those used clinically, increased coronary arterial flow in the unanesthetized trained dog (40) This is apparently due at least in part to coronary vasodilation Wégria and his associates (205) found that in

dogs anesthetized with chlorosane, large doses of coramine caused a momentary decrease followed by an increase in blood pressure and coronary arterial flow. The increased flow was of short duration, but outlasted the increase in blood pressure. Further, coramine increased blood flow through the perfused, isolated, fibrillating dog heart (37). The coronary sinus outflow of the intact, anesthetized dog (75, 185) and dog heart-lung preparation (185) was also increased. However, there is no evidence that coramine in the doses used clinically has a significant effect on the human coronary circulation.

*Metrazol* (cardiozol) increased coronary blood flow in the perfused, isolated, fibrillating dog heart (137), and heart-lung preparation (185), but the concentrations used were out of all proportion to that likely to reach the human heart. In non-toxic doses it was without effect on the coronary sinus outflow of the intact anesthetized dog (185). *Metrazol* is not now used clinically for its cardiac action. *Nicotine* diminished coronary flow in the isolated, perfused, human heart revived *post-mortem* (129). The decrease in blood flow was accompanied by a slight increase in heart rate and the amplitude of cardiac contraction. *Nicotine* was either without effect or caused mild constriction of isolated human (129), ox and pig (193) coronary arterial rings. Whether the concentration of *nicotine* used was comparable to that obtained from smoking tobacco was not remarked. *Camphor*, at one time a drug widely used as a reflex "stimulant" of the cardiovascular system, slightly increased coronary blood flow in the revived, isolated, perfused, beating human heart (129), and coronary sinus outflow in the dog heart-lung preparation (21).

Essex and his collaborators (46) observed that in a single experiment in the unanesthetized dog, *nembutal* increased coronary arterial flow. The addition of *glucose* to the perfusion fluid of the isolated, fibrillating heart increased coronary flow except in extreme concentrations impossible to reach therapeutically (137). On the other hand, 20 to 40 units of *insulin* added to fluid perfusing the isolated, fibrillating, dog heart also caused coronary vasodilation (37). The significance of these observations is not clear. In patients with coronary arterial disease and diabetes, *insulin* hypoglycemia may induce acute coronary insufficiency and death (135A). This may be due to impairment of the nutrition of the myocardium by prolonged hypoglycemia, or to an impairment of coronary blood flow not predicted by these experiments. We are not familiar with any studies of the effect of *glucose* upon coronary flow in the intact animal. Clinical experience is confused by the fact that hypertonic *glucose* is mildly diuretic.

The effect of increased concentrations of various ions upon coronary flow in the isolated, fibrillating dog heart has been studied by Katz and his associates. The heart was perfused with defibrinated blood to which calcium gluconate and *glucose* had been added. *Sodium chloride* (136), added to defibrinated blood to  $1\frac{1}{2}$  to  $2\frac{3}{4}$  times that normally present, significantly increased coronary flow for a few minutes. *Calcium chloride* (136) when added to a concentration  $1\frac{1}{3}$  to 24 times that usually present in defibrinated blood caused a prolonged increase in coronary flow even though in some instances the cardiac fibrillation became coarser or synergistic beating occurred. On the other hand, *calcium gluconate* (137) was without effect. *Potassium chloride* (136) caused vasodilation in low

concentrations and constriction in higher concentrations. However, the concentrations used represented an increase of many times in the level of extracellular plasma potassium, to an unphysiologic degree. *Magnesium sulfate* (37) caused a transient increase in coronary flow.

In these experiments, the changes in concentration of the ions studied was always much greater than the homeostatic mechanisms of the body permit. These data are therefore not applicable clinically. Studies in the intact animal would be most desirable.

**Histamine and Anaphylactic Shock** The action of *histamine* upon coronary vessels varies from species to species. Histamine increased coronary arterial inflow (130) and coronary sinus outflow (2) in normal, isolated, revived human hearts. On the other hand, the coronary flow of dilated human hearts was diminished by histamine (131). Isolated human coronary arterial rings of relatively large diameter were constricted by histamine (28, 129) while smaller isolated arteries were dilated (129). Since total flow depends more upon the diameter of the smallest rather than the largest blood vessels, these studies are not contradictory.

*Histamine* increased the dog's coronary flow whether measured in a perfused, isolated, fibrillating heart (126), the heart-lung preparation (155) or the anesthetized (205) or unanesthetized (46) intact animal. The coronary flow of the perfused, isolated, beating cat heart was also increased by histamine (1, 105, 147). On the other hand, the coronary flow of the isolated, beating, perfused rabbit (1, 105, 147) and guinea pig (212) heart was diminished by histamine.

Histamine is not used therapeutically in cardiac disease. However, Wiggers (210) suggested that histamine may be liberated at the margins of a potentially infarcted area, and thus might be important in favoring collateral flow. The action of histamine is also of interest because of the similarities between its effects and *anaphylactic shock*. Andrus and Wilcox (1, 212) studied coronary flow in the isolated, perfused, beating heart during anaphylactic shock. They used a modified Langendorff preparation in which the coronary arteries were perfused through the aorta. Coronary blood flow was measured in two portions. The major portion was drained from the right ventricle, and the remainder, the outflow from the left Thebesian vessels and any small leakage around the aortic cannula, from the left ventricle. Anaphylactic shock in animals sensitized to horse serum decreased coronary flow in guinea pig and rabbit hearts, and increased flow in cat hearts. These changes are the same as those produced by histamine in these species, corroborating the evidence that an *histamine-like* substance is released during anaphylaxis.

The introduction of serum (1) or defibrinated whole blood (127) of a different species diminished coronary flow in isolated cat and dog hearts. Since histamine is a vasodilator for both these species, it is doubtless not the substance in blood responsible for the vasoconstriction.

#### CORONARY BLOOD FLOW IN DISEASE STATES

**Hypertension** Since coronary blood flow cannot be measured *in situ* in man, one can only infer the changes which may occur in hypertension. Nor are we

familiar with any experiments in which coronary blood flow was measured in chronically hypertensive animals. However, in acute experiments coronary flow is roughly proportional to the arithmetic mean blood pressure at the root of the aorta (2). Diastolic blood pressure is relatively more important than systolic (179), all things being equal, an increase in diastolic blood pressure will be accompanied by an increase in coronary flow. During systole, coronary flow does not increase proportionately with aortic pressure, since the extravascular resistance to flow offered by the ventricular muscle increases concomitantly. In clinical hypertension, one would expect an increase in coronary blood flow. However, this may not compensate adequately for the increased cardiac work which hypertension imposes, nor for the decrease in the maximal capacity of the capillaries (198, 33) relative to the mass of muscle fibers in the hypertrophied hearts of patients with prolonged hypertension. In the absence of experimental proof, the changes in coronary flow in hypertension can only be conjectured.

Several studies of the action of the humoral mediators of experimental hypertension have been done. Hill and Andrus (112) and Lorber (139) observed that *angiotonin* caused a decrease sometimes followed by an increase in coronary flow in the isolated cat heart. Since the decrease was noted in a fibrillating heart, presumably vasoconstriction occurred. *Renin* did not affect coronary flow when added to the perfusing fluid, Ringer-Locks's solution. Elek and Katz (37) on the other hand observed both vasoconstriction and vasodilation in different experiments with the fibrillating dog heart perfused with blood containing angiotonin or renin. In the latter instance, the renin presumably combined with the substrate present in blood to form angiotonin. The significance of these experiments in relation to human hypertensive disease is not clear.

*Congestive Failure* When, during the course of cardiac disease, the left ventricle is unable to meet the demands upon it, so-called left ventricular failure supervenes. Blood dams back into the pulmonary circuit and pulmonary arterial pressure increases. The rôle of this increased pressure in the genesis of right ventricular failure is of considerable interest.

Gregg, Pritchard, Shipley and Wearn (93) increased pulmonary arterial pressure in the anesthetized dog by clamping the vessel and measured coronary arterial flow with a rotameter. They observed that the resultant increase in right intraventricular pressure was accompanied by increased coronary flow, particularly in the right coronary artery. This increase was during both systole and diastole and was always present unless the resistance to pulmonary arterial flow was severe enough to cause a considerable drop in aortic blood pressure. In these experiments the constriction was continued for 25 minutes. Whether the same results would have been obtained after prolonged pulmonary hypertension such as occurs clinically is not clear. In patients with coronary arterial disease, angina pectoris frequently diminishes when congestive failure appears. Perhaps this represents an increase in coronary arterial flow as right intraventricular pressure increases. Gregg and his associates did not explain the mechanism by which coronary arterial flow was increased. Possibly it is secondary to an increase in right auricular pressure which has been shown to cause reflex vasodilation (63).



When pulmonary arterial constriction is sufficient to decrease left ventricular output and aortic blood pressure, right ventricular failure follows (51). This is at least partly the result of decreased blood flow through the right ventricular muscle. Since coronary blood flow is directly dependent upon aortic pressure, it will decrease as aortic pressure decreases. Further, right ventricular coronary flow may be restricted because of increased resistance to venous drainage. The main venous drainage of the right ventricle is through channels other than the coronary sinus. As pulmonary arterial pressure rises relative to aortic pressure, the amount of blood draining through these channels decreases, and the venous drainage of the right ventricle is impeded (149, 150). Although the oxygen of the blood is more completely utilized by the ventricular muscle, as evidenced by a decreased oxygen content of the venous blood (150), the nutrition of the right ventricle is impaired, and severe dilation and cyanosis of the right heart appear. Visscher and Moe (150, 192) concluded that elevation of right intraventricular pressure accelerates cardiac failure, and that this is due to the restriction of coronary flow which occurs. They pointed out that, "The left side of the heart can carry enormous loads as in hypertension and in valvular disease for many years, whereas when the right ventricle works against increased loads the heart fails rapidly." They also noted Levine's observation (135) that patients with mitral stenosis have a better life expectancy if there is coincident hypertension. Presumably this is because the aortic hypertension may maintain the coronary blood flow to the right ventricle and thereby postpone the appearance of right ventricular failure.

The rôle of a deficient coronary blood supply in the development of cardiac failure was also emphasized by Kountz and Smith (131). They measured coronary arterial flow in revived hearts of persons who had died of cardiac insufficiency. In isolated heart and heart-lung preparations they observed that the total coronary flow of patients with heart disease was frequently greater than normal, especially when severe cardiac failure had occurred. Per unit weight of heart, however, coronary flow was less than normal. The lowest figures were observed in patients with arteriosclerotic heart disease. In contrast to the normal heart, the coronary flow of hypertrophied hearts increased only a negligible amount when the perfusion pressure was increased. As the heart dilated in failure, coronary arterial flow decreased. Studies of the variations in coronary flow throughout the cardiac cycle showed that in the normal heart, blood flow was maximal during diastole, but in the dilated heart, during systole. Kountz and Smith believed that hearts fail in chronic cardiac disease because the coronary blood flow is relatively inadequate due to the increase in muscle mass or constriction of the blood vessels.

Kountz and Smith also made the important observation that the response of the heart to drugs depends upon the state of the cardiac muscle. Thus histamine and the nitrites, which increase coronary flow in the normal isolated heart, decreased it in the dilated heart. These drugs increase the degree of cardiac dilation. Conversely, digitals and adrenalin, which reduce coronary flow in normal isolated hearts, increased flow in dilated hearts and at the same time decreased the degree of dilation. These data can be explained if cardiac dilation diminishes

coronary flow by stretching and narrowing the coronary vessels. Drugs which increase cardiac dilation would then decrease coronary flow, and those which decrease dilation would increase flow (131).

In general, then, heart failure occurs when the coronary blood supply becomes insufficient relative to the load placed upon it. The left ventricle is able to compensate for an increased load for long periods. Once left ventricular failure occurs, however, pulmonary arterial pressure rises. When the pulmonary arterial pressure becomes sufficiently high relative to aortic pressure, the coronary flow through the right ventricle is impeded, and the right ventricle fails.

*Coronary Flow in Valvular Heart Disease* The changes in coronary flow in aortic valvular disease can be predicted from a knowledge of the normal variation in flow during the cardiac cycle. During the latter half of systole the forward movement of blood is impeded by the peripheral resistance offered by the contracting ventricle. As the heart relaxes during diastole, coronary flow increases and is roughly proportional to the diastolic blood pressure. In *aortic insufficiency*, the blood pressure may fall very low during the latter part of diastole. One would predict that when this occurs diastolic coronary flow would be curtailed sharply. In *aortic stenosis*, on the other hand, the systolic blood pressure may be reduced, and at the same time the left ventricle must contract vigorously enough to expel blood through the stenosed valve. Therefore, in aortic stenosis, coronary flow would be restricted by the decreased systolic pressure and increased systolic resistance to flow.

Smith, Miller and Graber (179) produced *aortic insufficiency* in dogs by puncturing the aortic cusps with a wire introduced through the carotid artery. A slight rise in systolic and a sharp fall in diastolic pressure resulted. In these experiments, coronary sinus outflow was much curtailed. However, this is not an accurate measure of total coronary flow, nor is comparison of central and peripheral coronary arterial pressures, a technique with which Green (65) confirmed these experiments. In the heart-lung preparation, Davis (31) observed decreased coronary flow in both systole and diastole, as measured with the hot wire anemometer. On the other hand, in the intact dog Green and Gregg (68), recording coronary arterial flow with the orifice plate meter, reported that systolic flow was increased in aortic insufficiency. In severe aortic insufficiency this was not enough to compensate for the decreased diastolic flow, so that minute blood flow through the coronary arteries was decreased.

These studies help explain the frequency of sudden death in patients with severe aortic insufficiency (135). If a sudden demand is made upon the heart, the strong ventricular contraction may sharply reduce the amount of blood reaching the ventricular muscle during systole. This, followed by the curtailed flow of diastole, may result in death, perhaps by the precipitation of ventricular fibrillation or standstill. In our experience, sudden death with aortic insufficiency occurs more frequently in luetic than rheumatic heart disease. Perhaps this is because in syphilis the mouths of the coronary arteries are frequently narrowed and the coronary blood supply correspondingly impaired.

Green and Gregg (68) measured coronary flow in experimental *aortic stenosis* in the anesthetized dog, with an orifice plate meter. They observed that coro-

nary flow was decreased and that the reduction occurred almost entirely during systole. As Green (65) had pointed out previously, the systolic reduction in flow was due to the more gradual elevation of aortic pressure and the great increase in systolic peripheral coronary resistance in this disease.

One would expect the changes in coronary flow in *arterio-venous fistula* to be similar to those in aortic insufficiency. Apparently this has not been studied with the newer methods of measuring coronary flow. In experimental arterio-venous fistula, both coronary sinus outflow (179) and coronary arterial inflow, calculated from differential pressure curves (65) have been reported reduced. The latter studies indicate that, as in aortic insufficiency, the reduction in flow occurs during diastole.

Coronary blood flow in *mitral stenosis* has not been studied experimentally. Kountz and Smith (131) reported that the total coronary flow to a revived human heart with mitral valvular disease was reduced to about one-fourth of normal. Surprisingly, the right ventricle receives a greater share of the coronary flow than the left. In mitral stenosis, blood dams back through the pulmonary circuit and pulmonary hypertension results. Presumably the changes in coronary flow which follow are similar to those in experimental pulmonary hypertension. As we have seen, at first right coronary flow increases. When the pulmonary hypertension is severe enough, the coronary flow to the right ventricle diminished and right heart failure ensues. As Moe and Viischer have emphasized, the impairment of coronary blood supply which accompanies an increase in right intraventricular pressure is much greater than that accompanying an increase in left intraventricular pressure. This may be an important contributing factor to the more rapid course of cardiac failure in the patient with mitral rather than aortic disease.

*Hyperthyroidism.* In experimental hyperthyroidism, the coronary blood flow is increased. Essex and his associates (40) injected one mgm per kilogram of body weight of *thyroxin* into trained dogs. In two to four days these animals had increased pulse rates, decreased circulation times, and intense muscular tremors. The coronary arterial blood flow increased 132 to 244 per cent, as measured with the thermostromuhr in the unanesthetized animal.

In these experiments, then, hyperthyroidism was accompanied by an increase in coronary arterial flow. The mechanism is not clear. The increased flow is probably the resultant effect of a number of factors. Hyperthyroidism is accompanied by tachycardia, an increase in systolic blood pressure and possibly a decrease in diastolic pressure. In addition, the increased metabolism of the ventricular tissues may release increased amounts of metabolites which effect the caliber of the coronary vessels. Further, the cardiac output is increased, and this, as we have seen, results in an increase in coronary flow in the intact animal.

*Anemia.* We are not familiar with experimental studies of the effect of anemia on the coronary circulation. One might predict that in moderate anemia the decreased oxygen carrying capacity of the blood would be compensated by the increased flow resulting from the decreased viscosity of the blood and the increased cardiac output which occur *pari passu*. With severe anemia, however,

the cardiac tissues would become anoxic and despite the resultant vasodilation, myocardial damage would occur. Such changes have been observed clinically (128)

*Myocardial Ischemia* After temporary occlusion of a coronary artery, an increase in coronary blood flow follows almost immediately. Gregg and Green (68, 87) observed the increase during both systole and diastole whether the heart was perfused at a constant or a pulsatile pressure. In the heart *in situ*, ischemia increased blood flow despite a fall in aortic blood pressure, indicating that peripheral resistance to flow decreased both in systole and diastole. Experiments of Katz and Lindner (124) demonstrate that this decrease in peripheral resistance after ischemia was due at least partly to vasodilation. The increase in coronary flow after ischemia is profound. As short a period of ischemia as 3 to 5 seconds increased coronary flow (70), and periods as long as two minutes caused a subsequent increase in coronary flow of as much as 350 per cent.

The great increase in coronary flow after temporary myocardial ischemia may be due to the accumulation of metabolites either normally removed by the blood or oxidized locally. Katz and Lindner (125) suggested that this coronary vasodilation may serve to increase the blood supply when myocardial needs are not met by the existing coronary flow. Perhaps in man this vasodilation may modify the effects of the relative ischemia which may appear during such episodes as exercise or angina pectoris.

*Collateral Circulation* Studies of the human heart at autopsy have demonstrated that an extensive collateral circulation may develop to compensate for the gradual narrowing of the coronary arteries by arteriosclerosis (20). Only recently have similar anastomotic connections been established experimentally, for the gradual restriction of the circulation which occurs in human disease is difficult to duplicate. The usual experimental procedure is to occlude a coronary arterial branch partially or completely. This slows or stops the circulation at a single point. Actually, in man, complete closure of a coronary vessel when it occurs is almost always preceded by a prolonged period during which the vessels have been narrowed by arteriosclerosis.

Potentially, extensive anastomotic connections exist in the heart. Spalteholz (180) demonstrated connections among the various coronary arteries, using dye techniques, and this has been corroborated by Prinzmetal and his associates (163). More recently, Blumgart, Schlesinger and Davis (20) observed that in the normal human heart, regardless of age, these anastomoses are among vessels smaller than 40 micra in diameter, that is, chiefly among capillary and pre-capillary vessels. Wearn and his associates (199) described connections between the coronary arteries and the lumen of the heart directly through "arterio-luminal" vessels and indirectly through myocardial sinusoids. The coronary bed is also connected with the cardiac lumen by Thebesian vessels. In addition, in the human heart, extracardiac anastomoses normally exist with the blood vessels in the fat at the base of the heart (116).

As Wiggers (210) stressed, the mere existence of these anastomoses does not mean that they are functionally adequate. Pratt (162) was able to sustain the contractions of a cat heart by retrograde flow through coronary veins or The-

besian vessels. However, the cat heart can be maintained with a minimal blood supply, and indeed Pratt noted that virtually no blood circulated in his experiments. Further, in these studies, no load was placed upon the heart. If an adequate collateral circulation exists normally, one would expect that after a coronary artery is ligated, peripheral to the ligature, blood would flow in a retrograde direction from other coronary vessels or the ventricular cavities. Actually, Eckstein, Gregg and Pritchard (35) observed that after occlusion of a large coronary artery in the dog the retrograde flow was only 0.5 to 5.8 cc per minute, which is much less than normal. When all the coronary arteries were ligated, virtually no retrograde flow could be measured distal to the ligatures (181). That is, virtually no blood reached the ventricular muscle through those vessels which connect the coronary vascular bed with the ventricular cavities.

In acute experiments the small retrograde flow distal to the point of occlusion of a coronary artery is not adequate to maintain ventricular muscular contraction. Tennant and Wiggers (188) reported that ventricular muscle ceased to contract within as short a time as one minute after the artery supplying it was occluded. Although a collateral circulation may be present in the dog heart (19, 175), Beck and Mako (16) found that the mortality rate after ligation of the descending branch of the left coronary artery was 80 per cent.

When the coronary occlusion is not fatal, new collateral channels develop to nourish the ischemic tissues. Wiggers (210) described three types of such compensatory anastomoses. New intercoronary communications may develop, extracardiac communications may form, and the arterio-luminal channels may enlarge. Eckstein, Gregg and Pritchard (35) observed that retrograde flow distal to the ligation of the descending branch of the dog's left coronary artery increased, for example, from 3.4 to 6.8 cc per minute within 48 hours, and to 18 cc per minute within a week. None the less, it was seven weeks before contraction was noted in the muscle formerly supplied by the occluded vessel.

After partial or gradual occlusion of a coronary artery, an extensive collateral circulation may develop which will protect the involved area from subsequent complete occlusion of the principal artery. Mautz and Gregg (90, 144) studied the coronary circulation of the dog 2 to 12 months after progressive occlusion of the right or the circumflex or descending branch of the left coronary artery. In many dogs, sufficient collateral circulation developed to maintain essentially normal myocardial activity in the zone previously made ischemic. Flow in the arteries distal to complete occlusion averaged 30 to 40 cc per minute. The blood was arterial in composition and apparently adequate to maintain contraction of the muscle normally supplied by the occluded artery. Part of this new collateral flow was from other, unoccluded coronary arteries. Apparently, however, blood reached the ischemic area through other channels as well. Probably some came through arterio-luminal vessels from the ventricular cavity. And, as Robertson (170) observed in dogs in which the coronary arteries had similarly been occluded slowly, extracardiac vascular channels may develop through the pericardium to the heart.

Blumgart and his associates (19) studied the development of collateral cir-

culatation after coronary occlusion in the young pig When the right coronary artery or the descending branch of the left was narrowed to the point where the lumen was less than 15 per cent of its original diameter, the pig died within a few hours After less drastic constriction, a collateral circulation developed rapidly, demonstrable by the injection of dyes into the arteries 3 hours to 7 days later Within this time complete occlusion of the coronary artery still resulted in immediate death However, 12 days after coronary arterial narrowing, a rich anastomotic circulation had developed between the major coronary arteries, and complete occlusion of the originally narrowed artery was no longer followed by myocardial infarction and death This development of an extensive collateral circulation in the presence of coronary arterial constriction is strikingly similar to that observed in human hearts *post mortem* (20) Presumably, when coronary arterial narrowing occurs, a compensatory anastomotic circulation develops which may be adequate to maintain the myocardium under ordinary conditions, and indeed after a subsequent complete occlusion, though with a diminished reserve

To increase the collateral circulation subsequent to a narrowing or occlusion of the coronary vessels, various expedients have been used These include the administration of vasodilator drugs, ligation of the venous drainage of the heart, and anastomosing various tissues to the heart

Once coronary occlusion has occurred, little evidence exists that the administration of drugs will assist materially the establishment of adequate anastomoses Manning, McEachern and Hall (141) believed that concomitant with coronary arterial occlusion, vasoconstriction occurs in the uninvolved coronary arteries They observed that the mortality of dogs after coronary arterial occlusion was reduced by fully anesthetizing the animals (145) Sectioning the stellate ganglia (25) and upper five thoracic ganglia on the left or bilaterally (145) also decreased mortality When one coronary artery was ligated, coronary flow was reduced in an uninvolved coronary artery in the normal dog, but not in the ganglionectomized dog Further, LeRoy and his associates (134) observed that atropine, which blocks the transmission of parasympathetic impulses, reduced the immediate mortality of dogs after coronary arterial ligation

Fowler, Hurevitz and Smith (52) believed that aminophylline decreased muscular cyanosis and the size of the subsequent infarct distal to the ligation of a coronary artery Theobromine sodium acetate administered parenterally has been reported to reduce immediate mortality in dogs subsequent to ligation of a coronary artery, but aminophylline was without significant effect (134) Papaverine is said to decrease mortality after coronary arterial ligation from 75 to 50 per cent (146) All these drugs may act by reducing the degree of vasoconstriction of the unaffected coronary vessels, and papaverine, in addition, may have a sedative effect (146) On the other hand, Gold, Travell and Modell (62) observed that aminophylline did not influence favorably the size of infarcts in the cat Wiggers and Green (211) were unable to demonstrate any favorable effects from the inhalation of oxygen, carbon dioxide or amyl nitrite, or from the intravenous administration of nitrites, various theophylline preparations, adenylic

acid or adrenalin. Nor did quinidine sulfate (177) significantly affect mortality after coronary arterial ligation. In general, the evidence that drugs can influence the development of myocardial infarction after coronary arterial occlusion is equivocal at best (22).

Ligation of the coronary sinus or coronary veins has been suggested as a means of increasing the blood supply to an area rendered ischemic by arterial occlusion (100, 170, 191). Clinically, angina pectoris is frequently alleviated with the onset of congestive heart failure as the coronary venous pressure rises (191). Robertson (170) reported that occlusion of the principle venous drainage of the heart protected 3 of an unspecified number of dogs from the effects of occlusion of all the coronary arteries. Large collateral channels formed with extracardiac vessels, apparently the Thebesian vessels did not contribute to survival. Gross and his associates (100) did not observe a reduction in immediate mortality after occlusion of the left coronary artery when the coronary sinus was ligated first, but the size of the resultant infarct was decreased. Partial occlusion of the coronary sinus lowered the mortality after subsequent occlusion of the descending branch from 53 to 31 per cent as well as decreasing the size of the infarct.

In a large series of dogs, Beck and Mako (16) observed that occlusion of sinus or great coronary vein a week or more before ligation of the descending branch of the left coronary artery lowered the mortality rate from 80 to 54 per cent. A greater degree of protection was reported by Fauteux (48) when the interval between ligation of the principle cardiac venous drainage and ligation of the descending branch of the left coronary artery was prolonged to a year. Unlike Gross and his associates (100), Beck and Mako reported that venous occlusion itself was virtually without mortality. Further, after partial coronary arterial occlusion, the resultant infarct seemed to be somewhat smaller if the main coronary venous channels were simultaneously occluded. Gregg and his associates studied the effects of coronary sinus ligation on coronary flow. In acute experiments simultaneous ligation of the coronary sinus increased retrograde flow distal to a coronary arterial ligature from one to as high as 39 cc per minute (83). That is, simultaneous ligation of the coronary sinus increased the blood supply to the ventricle after coronary arterial ligation. However, the blood which flowed distal to the ligature was deeply venous, containing only 3 to 4 volumes of oxygen per 100 cc of blood, a concentration insufficient to support ventricular contraction. Therefore the myocardium distal to the ligature quickly lost its ability to contract. Nor did ligation of the cardiac vein prevent loss of contractility by the ischemic area. Gregg and Dewald (81) concluded that acute occlusion of the major portion of the heart's venous drainage does not aid the coronary circulation.

The increased retrograde flow observed in acute experiments did not occur if the veins were ligated some time before the artery (190). Immediately after coronary sinus ligation the cardiac venous pressure rose, for example from 14/5 to 54/12 mm of mercury. Within a month, however, the pressure fell to 20/10 mm of mercury, presumably because other venous channels were able to relieve the excessive pressure. When a coronary artery was now occluded, the ret-

rograde flow distal to the occlusion was at most 5 cc per minute, compared to 39 cc if the coronary sinus and artery were occluded simultaneously. The myocardium distal to the ligature ceased contraction within 30 seconds. None the less all the dogs subjected to this two stage operation survived, although most dogs in which arterial ligation alone was performed died. Thirty days after the second operation the myocardium distal to the ligature was observed contracting, and retrograde flow had increased to 42 cc per minute of oxygenated blood. Although the clinical significance of these experiments is not clear, one must conclude that coronary sinus occlusion preceding arterial ligation improves coronary blood flow. Interestingly enough, coronary occlusion is said to be uncommon in patients with rheumatic heart disease (99), perhaps because of the chronically elevated venous pressure in these patients. These experiments do not suggest that ligation of the coronary sinus would be of value once myocardial infarction has occurred. The value of such an operation in the patient with angina pectoris who has not yet had obvious infarction is debatable. Fauteux and Palmer (49) observed relief of pain in 6 patients with angina pectoris in whom the great cardiac vein was ligated just below the coronary sinus, but the ultimate course of these patients was not described.

A third method of improving the coronary circulation is the establishment of new anastomotic connections between extracardiac and coronary blood vessels. The experimental basis of such procedures has been reviewed critically by Burchell (24). Robertson (170) described the development of anastomotic branches from the pericardium subsequent to slow experimental coronary occlusion in the dog, and Moritz, Hudson and Orgain (81) observed similar communications in the human heart. Such extracardiac anastomoses may be produced surgically in the dog heart by various techniques. Beck and his associates (14, 17) established communications between coronary and extracardiac vessels by anastomosing fibrous pericardium, pericardial fat, the skeletal muscle of the chest wall, or the omentum to the myocardium. These communications could be shown to be patent by injection of dye or radio-opaque material. The development of collateral vessels was enhanced by partial occlusion of the coronary arterial circulation. Subsequent to the establishment of the new circulation, occlusion of the coronary arteries in several stages did not produce infarction. More important, the mortality subsequent to complete ligation in one stage of the right or descending branch of the left coronary artery was strikingly diminished. Although Burchell (24) questioned the efficacy of such anastomoses in dogs, their value was confirmed by Anrep (2) who sutured the dog's triangularis sterni muscle to the myocardium, and by O'Shaughnessy (156, 157) and Rienhoff (168) who joined omentum to the myocardium. A collateral circulation may also be established by suturing the lung to the heart (159). The collateral circulation established by inducing adhesions between the heart and surrounding structures by the introduction of foreign irritants may also act as protection against coronary arterial ligation in the dog. Thus vascular adhesions between the heart and surrounding structures have been described after introduction of aleuronat (109, 110, 159), asbestos (173) or talc (189).



Extensive studies of Schildt, Stanton and Beck (173) indicate the probable superiority of powdered asbestos

It is beyond the province of this paper to discuss the clinical value of operations designed to improve the coronary circulation. Strieder (186) recently reviewed the results of such operations. The pectoral muscles (14) or omentum (158, 187) have been sutured to the myocardium. The latter procedure may be complicated by diaphragmatic hernia. Or foreign substances have been introduced into the pericardial cavity to induce a collateral circulation between the heart and surrounding tissues (15, 186, 189). Although symptomatic relief may follow these procedures (50, 189), the operative mortality rate is relatively high. The rôle of surgery in the relief of coronary arterial insufficiency is yet to be determined.

In summary, numerous potential anastomotic connections exist in the heart. These are inadequate to supply the myocardium subsequent to sudden complete coronary arterial occlusion. However, after gradual arterial occlusion, these collateral vessels dilate and then may protect against a subsequent complete occlusion. Drugs are of questionable value in increasing the volume of collateral circulation. Experimentally, occlusion of the principle coronary venous drainage previous to arterial occlusion, or anastomosis of extracardiac and coronary blood vessels, may improve the coronary circulation. The clinical utility of these procedures has not yet been established.

#### SUMMARY

Blood flow in any organ is inversely proportional to the peripheral resistance and proportional to the head of pressure, i.e., pressure at the mouth of the artery. Peripheral resistance is a function of the state of constriction of the arterio-capillary tree, the viscosity of the blood and, to some extent, of the pressure at the venous end of the capillaries.

The circulation of the heart differs from that of other organs. Numerous anastomoses exist between the coronary vessels and the ventricular cavity. The peripheral resistance to flow varies throughout the cardiac cycle as the ventricular muscle contracts and relaxes. Accurate measurement of coronary flow is most difficult. No method is available to measure the flow through the coronary capillaries themselves. Measurement of coronary sinus outflow, a widely used technique is inadequate because this is not a constant fraction of total coronary flow. The outflow of the pulmonary arteries may be used as a measure of coronary flow in the perfused, isolated heart, and heart-lung preparation, but not in the intact animal. In the latter the most accurate technique available is to measure coronary arterial inflow, either with a thermotromuhr, a rotameter or an orifice plate meter, details of which have been described. To learn the responses of the intact animal, coronary flow must be studied *in situ*. The factors determining these responses may be analyzed in the isolated heart or heart-lung preparation. However, discretion must be used in transferring information from artificial preparations to the intact animal, from species to species, and even among individuals of the same species.

Apparently reliable studies indicate that the minute volume of coronary blood flow in the quietly beating heart is about 60 to 175 cc per 100 grams of heart per minute. About one fifth flows through the right coronary artery, one half through the circumflex branch and the remainder through the anterior descending branch of the left. As in other organs, blood flow is directly dependent upon arterial pressure. During systole, the forward movement of blood is resisted by the contracting ventricular muscle. The flow is therefore more directly proportional to diastolic rather than systolic blood pressure. On the other hand, increasing coronary venous pressure decreases inflow particularly into the left coronary artery. An increase in rate of the denervated heart increases coronary flow if the initial rate is slow, is without effect in the middle range, and decreases flow at high rates. Although reflexes modify this in the intact animal, clinical tachycardias may impair coronary flow seriously. Asphyxia and anoxia profoundly increase coronary flow, probably because of the accumulation of normally oxidized vasodilator metabolites and because of changes in heart rate, blood pressure and the strength of ventricular contraction.

In the denervated heart cardiac output *per se* does not influence coronary flow. However, flow during systole varies inversely with the strength of ventricular contraction because of the concomitant compression of the coronary vessels. Therefore coronary flow is impeded at the end of systole. It increases rapidly early in diastole as ventricular compression of the vessels diminishes, only to decrease again as the aortic pressure falls. Coronary arterial flow again increases as the aortic pressure rises early in systole. Since left ventricular contraction is stronger than right, the systolic restriction of flow is greater in the left than the right coronary artery, and indeed, with vigorous contractions may be sufficient at the end of systole to stop flow momentarily. On the other hand, coronary sinus outflow is maximal during ventricular systole and is sharply reduced or ceases during diastole. The coronary venous blood returns to the lumen through several routes. The major portion of the flow from the left ventricle drains through the coronary sinus, and that from the right, through the anterior cardiac veins into the right auricle. However, the proportion draining through each vessel varies considerably. Under ordinary conditions little blood reaches the lumen through the Thebesian veins and sinusoidal vessels. When right intraventricular pressure is high relative to coronary arterial pressure, retrograde flow may occur, but is probably of little importance since the oxygen content of right ventricular blood is low.

The caliber of the coronary blood vessels is under the control of the autonomic nervous system. The close anatomic association between the sympathetic and parasympathetic nerve trunks makes study of the effects of nervous stimulation or section difficult. *Acetylcholine*, the parasympathetic neurohumor, increases coronary flow in the dog, but its action in cat and rabbit hearts is not certain. Sympathomimetic adrenalin increases coronary flow in the intact, innervated dog heart, and apparently dilates the coronary arteries of most species. In cats and man adrenalin increases coronary flow.

The effect of vagal stimulation on the caliber of the coronary vessels is not

clear In the fibrillating heart the vagus dilates the vessels, as it does elsewhere in the body In the isolated beating heart and the intact animal the coronary vessels are constricted The effect of sympathetic nervous stimulation varies in the fibrillating heart, but in the isolated beating heart, the heart-lung preparation and the intact animal coronary blood flow is increased. In the dog the vagi are in a state of continual tonic activity regulating coronary flow, but apparently sympathetic tone is negligible Correspondingly, parasympathetic nerve fibers ramify to reach the smallest fibers, whereas few sympathetic fibers extend beyond the larger vessels These experiments do not elucidate the degree of tonic nervous control in man

In general, weak stimulation of afferent nerves increases, and stronger stimulation decreases coronary sinus outflow Distention of the stomach or peritoneal cavity usually decreases coronary arterial flow, perhaps accounting for post-prandial anginal pain Exercise, cutaneous pain and cooling of the skin may increase flow, but apparently not enough to compensate for the concomitantly increased cardiac work, for these stimuli may induce anginal attacks A rise in cerebral blood pressure diminishes, and a fall increases coronary flow, an effect apparently mediated through the carotid sinus

The pharmacologic action of various drugs upon the coronary circulation has been studied extensively but in most instances the concentrations of drugs used were far out of proportion to those likely to reach the human heart and the effects of rate, heart volume and arterial pressure were not controlled Variations in the response of different species and among individuals of the same species must be stressed In concentrations comparable to those used clinically, the nitrites, papaverine, ephedrine, atropine and perhaps morphine increase coronary flow The xanthines, coramine and metrazol increase coronary flow only in concentrations far greater than those used therapeutically Pituitrin and its pressor principal pitressin cause severe and prolonged coronary vasoconstriction Digitalis and allied compounds are without effect in non toxic doses, but decreases coronary flow in toxic concentrations Quinidine does not affect coronary flow Histamine increases coronary flow in human, dog and cat hearts, and decreases flow in guinea pig and rabbit hearts, paralleling the effect of anaphylaxis in the last three species

The coronary blood flow of chronically hypertensive animals has not been studied In acute experiments, coronary flow increases as the blood pressure increases Evidence concerning the action of angiotonin and renin on coronary flow is conflicting In experimental hyperthyroidism, coronary flow increases

An hypothesis may be attempted to explain the genesis of congestive heart failure Congestive failure may occur when the coronary blood supply is insufficient relative to demand The left ventricle can accommodate an increased load of work for long periods When it fails, pulmonary arterial pressure rises At first this results in an increase in coronary flow particularly through the right coronary artery, possibly mediated reflexly When pulmonary arterial pressure rises sufficiently relative to aortic pressure, coronary flow through the right ventricle is impeded and right ventricular failure rapidly ensues

In experimental aortic stenosis, ventricular contraction is more vigorous than normal, and coronary flow is reduced, particularly during systole. On the other hand, in aortic insufficiency and arterio-venous fistula, the flow is sharply reduced during diastole, as the blood pressure falls. Coronary flow in mitral stenosis has not been studied experimentally. One would expect, as pulmonary arterial pressure increases, an increase followed by sharp restriction of right coronary arterial flow, and right heart failure.

Temporary myocardial ischemia is followed by vasodilation and a profound increase in coronary blood flow. As the coronary arteries narrow in disease states, a compensatory collateral circulation may develop. Although these channels do not function normally, potentially extensive anastomoses are present between the various coronary arteries, between the coronary vessels and the ventricular lumen, and between the coronary and extracardiac vessels. After gradual arterial occlusion these channels may dilate and protect the heart against a subsequent complete occlusion. Drugs are of questionable value in increasing the volume of collateral circulation. Experimentally, occlusion of the principal coronary venous drainage previous to arterial occlusion or anastomosis of extracardiac and coronary blood vessels may improve the coronary circulation. The clinical utility of these procedures has not yet been established.

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# HUMAN TOXOPLASMOSIS

## A CLINICOPATHOLOGIC STUDY WITH PRESENTATION OF FIVE CASES AND REVIEW OF THE LITERATURE\*

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## INTRODUCTION

Toxoplasma is generally regarded as a protozoan parasite, although its exact classification is as yet not definitely determined. The microorganism was first described by Nicolle and Manceaux (49) in 1908 in the gondi, a North African rodent, and independently in the same year by Splendore (81) from Brazil in the rabbit. Toxoplasma has been confused with other protozoan parasites, particularly Encephalitozoon, Leishmania and avian malaria.

Since its original description over thirty years ago, spontaneous infections with Toxoplasma have been reported in a large number of species of mammals, reptiles and birds from many parts of the world, including every continent. It was not until 1923, however, that Jankú (28) reported the first instance of human infection. The disease occurred in an infant as an encephalomyelitis with chorioretinitis. Jankú described the microorganism but was unable to identify it. Subsequent morphologic studies (98) have established the identity of Jankú's case and it is now accepted as the first reported case of human toxoplasmic infection. The second case of human infection with Toxoplasma was reported by Torres (87) in 1927. The disease occurred in an infant and at that time the parasite was classified as an encephalitozoon, although Toxoplasma was considered. In 1937 Wolf and Cowen (97) described the third case with complete clinical and pathologic studies. The disease in this case occurred in an infant who had internal hydrocephalus, temperature elevation, a rapid pulse, hyperactive reflexes, convulsive seizures and bilateral chorioretinitis that was restricted to the region of the macula. Pathologic study of the brain, the spinal cord and the retina from both eyes disclosed many granulomatous lesions in these tissues containing intra-



and extracellular microorganisms morphologically similar to *Toxoplasma*. Two years later the same authors collaborating with Paige (99, 100) described a case with similar clinical manifestations. In this instance the microorganism was recovered by the intracerebral inoculation of rabbits and mice with tissue removed from the brain at autopsy. Subsequent immunologic studies showed cross-immunity with a known strain of *Toxoplasma* previously isolated from laboratory animals and conclusively proved the identity of the parasite. Careful comparative studies of the recovered organism with those observed in the previously reported cases established without question the identity of the causative agent.

Since the report of Wolf, Cowen and Paige (100) fifteen other cases of human infection with *Toxoplasma* having pathologic study have appeared in the literature, making a total of eighteen cases to date<sup>1</sup>. Thirteen have occurred in infants, one in a child 6 years of age and four in adults. In four instances *Toxoplasma* was recovered and identified biologically by inoculation of the diseased tissues into laboratory animals. The other fourteen cases have had morphologic studies in which the organisms have been identified in tissue sections.

In 1940 Pinkerton and Weinman (62) reported a fatal case of toxoplasmic infection occurring in a 22-year-old Peruvian laborer. The clinical and pathologic observations were obscured by a concomitant infection with *Bartonella bacilliformis*. A year later Pinkerton and Henderson (63) described two additional cases of toxoplasmosis, both occurring in adults. The disease in each case occurred as an acute febrile disease with a maculopapular rash involving the whole body except the scalp, the palms of the hands and the soles of the feet. Death occurred in six days in one instance and in eighteen days in the other. The clinical course observed in both patients strikingly resembled the typhus-spotted fever group of diseases. They suggest that ticks might be the vector of the disease since a history of tick bites was obtained from each of the patients.

In 1940 Sabin (71) described a fatal case of clinically atypical encephalitis in a six year-old child. The outstanding clinical features were generalized convulsions, fever, pleocytosis and disorientation without signs of meningeal involvement. Inoculation of a fresh suspension of brain tissue produced toxoplasmic infection in white mice and the organism was found in sections of the brain of the patient after a long search.

Recently we have had opportunity to study a case believed to be the infantile type of toxoplasmic encephalomyelitis. Following this stimulation to our interest in the subject, the 10,000 autopsies recorded in this department were reviewed with the purpose of identifying other cases of this disease not previously recognized. Our search was rewarded by the finding of five cases, none of which had been previously recognized as *Toxoplasma* infections. These cases were

<sup>1</sup> Since the preparation of this manuscript there have been reported 2 more probable cases of human toxoplasmosis occurring in adults

1 TOMLINSON, W. J. Human chronic toxoplasmosis. [Am J Clin Path 15 123, 1945]

2 KEAN, B. H. AND GROCUTT, R. G. Sarcosporidiosis or toxoplasmosis in man and guinea pig. Am J Path 21 467, 1945

listed under such diagnoses as "chronic meningitis," "syphilitic meningitis" and "encephalomalacia with calcification." Although *Toxoplasma* has not been biologically identified in any of the cases, microorganisms morphologically similar to *Toxoplasma* have been demonstrated in tissue sections in characteristic lesions in the central nervous system. This we feel is sufficient evidence unequivocally to establish the disease as toxoplasmosis. The present report is a clinicopathologic study of these five cases. In order to broaden the study and better evaluate the problem of this relatively new and interesting human protozoal disease all of the previously reported cases of toxoplasmosis have been collected and reviewed.

## II. REPORT OF CASES

*Case I* M B (Children's Hospital, St. Louis, Mo., #F-1600) a three-day-old white female infant was admitted to the St. Louis Children's Hospital on August 4, 1929 and died the same day.

*Chief complaints.* Those given by the parents were bleeding from the navel, mouth, and rectum.

*Family history.* The patient's mother was 21 years old, the father 24 years of age. Both were in good health. There was another child in the family, a boy aged 20 months who was reportedly normal and in good health. There was no family history of tuberculosis, syphilis or diseases usually considered as familial.

*Past history.* The child was a full term infant delivered spontaneously by a midwife and weighed  $6\frac{1}{4}$  pounds at birth. Cyanosis was noted at birth but the child responded well to resuscitation.

*Present illness.* The patient had been spitting small amounts of blood since birth and had always passed a small amount of blood with her stools. On the day of admission her navel began to bleed necessitating the application of three or four dressings. It was also noted that the patient had been jaundiced since birth and that she had many purpuric spots over the entire body.

*Physical examination.* At the time of entry to the hospital the infant was fairly well developed, was intensely jaundiced and had numerous small purpuric spots on the skin. The circumference of the head was 34.5 centimeters. The shape of the head was normal and the anterior fontanelle was 2.5 centimeters in width. The posterior fontanelle was opened and measured 1 cm. in diameter. A purulent discharge was noted in both eyes and there was a small amount of blood in the mouth. The ears and nose were normal. The chest was symmetrical and the expansion was equal on both sides. Vesicular breath sounds and normal resonance were heard over both lung fields. Examination of the heart was negative. The abdomen was slightly distended and there was a small amount of blood oozing from the umbilicus. All of the reflexes were equal and present and no pathologic ones were elicited. The clinical diagnosis at that time was hemorrhagic disease of the newborn. Because this diagnosis was made on admission 40 cubic centimeters of whole blood from the father were given to the infant in the admitting room. Later the same day a second transfusion of 60 cubic centimeters of whole blood was given in the ward. The patient died

during this second transfusion Urinalysis and blood counts were not performed The patient's temperature was always subnormal, varying from 36.4°C to 36.8°C

*Autopsy* Washington University Autopsy #3846 The body was that of a white female infant weighing 2.5 kilograms and measuring 45 cm. in length The skin and sclerae were markedly icteric and there were numerous large ecchymotic spots over the entire body, which were most prominent on the face, neck and upper thorax. A small amount of sanguineous fluid was present in the nose and in the mouth The anterior fontanelle was closed but there was considerable bulging in this area Several partially healed puncture wounds were noted in the region of the anterior fontanelle All of the superficial lymph nodes were palpable and prominent The abdomen was moderately distended The stump of the umbilical cord had not been removed, it was dry and crusted with dark red blood The liver was enlarged and extended 4 cm. below the costal margin The spleen was enlarged and there were many fine fibrous adhesions between the spleen and the adjacent viscera The peritoneum contained many foci of hemorrhage and all of the abdominal viscera were discolored a light yellow There was no free fluid in the pleural cavities but there were numerous subpleural hemorrhages Small focal areas of atelectasis were seen when the lungs were sectioned The spleen weighed 60 grams and on section the malpighian bodies were poorly visualized Examination of the gastrointestinal tract revealed focal hemorrhages in the mucosa of the stomach and of the small and large intestines They were most numerous in the region of the cecum and the ascending colon The liver weighed 180 grams and nothing remarkable was noted on section except its intense yellow color

When the calvarium was removed and the dura mater opened, a large amount of yellow fluid escaped under pressure Gross examination of the brain disclosed a marked loss of brain tissue in the cerebral hemispheres, the cortex being reduced to a thin wall of tissue that in many regions measured only a few millimeters in thickness Small white nodules were noted in the subarachnoid space Sections through the brain revealed a marked dilatation of the lateral and third ventricles.

*Microscopic examination* A section taken from the right kidney revealed several small foci of destruction of kidney tubules In these regions there were scattered lymphocytes, macrophages and occasional plasma cells. Sections of lung disclosed many focal areas of recent hemorrhage and in one area there was a small focus of lymphocytes and plasma cells The interlobular septa and the subpleural connective tissue were edematous The myocardium was infiltrated with small lymphocytes. These were found between the individual muscle fibers and were most prominent near the epicardial surface Small clumps of organisms each containing a definitive nucleus and cytoplasm were found within the muscle cells (Fig 9) There was no cellular reaction immediately around the parasites. A section taken from the small intestine disclosed many focal hemorrhages into the submucosal tissue without cellular reaction A section of liver

showed many large elongated masses of inspissated bile lying in the liver cells and in many instances between the liver cells. The liver also showed a moderate amount of extramedullary hemopoiesis.

In a section of the brain taken from the markedly thinned cerebral cortex there was complete destruction of all of the nerve cells with only large masses of glial cells remaining. On the ventricular surface there was a granulomatous type of reaction characterized by focal accumulations of macrophages, lymphocytes and plasma cells. In the granulomatous tissue there were numerous deposits of calcium. In some regions there was complete calcification of the exudate, forming a large calcified mass. Several small extra- and intracellular bodies identified as *Toxoplasma* were found in the section.

*Pathologic diagnoses* These were toxoplasmic encephalomyelitis, internal hydrocephalus, focal granulomas in the kidneys, inspissated bile in the liver cells, generalized icterus, focal hemorrhages in the skin, pleura, peritoneum, mucosa of the gastrointestinal tract, interstitial pneumonia and interstitial myocarditis.

#### *Summary of case*

A three-day-old infant, who had been jaundiced since birth and exhibited marked hemorrhagic tendencies manifested by purpuric spots, bleeding from the mouth, navel and rectum, was admitted to the hospital and died on the same day. At necropsy internal hydrocephalus, focal calcification in the brain, interstitial pneumonia and interstitial myocarditis were the principal lesions. Organisms morphologically identical with *Toxoplasma* were found in the brain, kidney and myocardium.

#### *Comment*

Sufficient time was not available for adequate clinical study of this case but it illustrates some of the manifestations which a severe infection of this type may produce. The hemorrhagic tendencies noted are not infrequently encountered in infants with toxoplasmic infection. The exact mechanism of the bleeding is not clear but it is probably a combination of two distinct phenomena. The first is the destruction of the cellular elements of the blood and suppression of their formation in the bone marrow, particularly of red blood cells and platelets. The second is the action of the parasite on the blood vessels, principally the capillaries. *Toxoplasmas* have frequently been identified within the endothelial cells of blood vessels, particularly the capillaries and small arterioles and venules. Jaundice is a not infrequent occurrence in infants with severe widespread infections. The lesions in the lungs and myocardium and the identification of parasites in the kidney give supportive evidence that the infection was generalized and not confined to the central nervous system. Evidence is also present to enable us to concur with the observations of Wolf, Cowen and Paige (102) that the inception of the disease may occur in utero. The nature of the pathologic changes observed in the central nervous system consisting of widespread destruction of brain sub-

stance with ghosis and calcification clearly indicate that the lesions were present and active before birth

*Case II* B.B (Children's Hospital, St Louis, Mo., #K-2532) a seventeen-day-old white male infant was first admitted to the St Louis Children's Hospital on November 19, 1934 and was discharged November 27, 1934

*Chief complaints* The infant had been jaundiced and had vomited frequently since birth

*Family history* The mother and father were living and well There had been a sister who died of dysentery at ten months of age A second sister, now two years old, was living and in good health The child that died also had jaundice which cleared up in two to three weeks after birth. There was no history of chronic illness or familial disease

*Present illness* The vomiting had become much worse during the four days prior to admission to the hospital. In the opinion of the infant's mother the jaundice had become progressively less severe since birth The bowels had moved two or three times a day It was stated that the infant vomited following each feeding and that vomiting was of the "projectile type" There had been no chills, fever or convulsions. The infant was breast fed until four days before admission, at which time he was given cow's milk and Karo formula

*Physical examination* Inspection disclosed an intensely jaundiced seventeen-day-old infant who was acutely ill and lying listlessly in bed. The child would cry out at infrequent intervals Respirations were of the Cheyne-Stokes type with several irregular deep breaths followed by long periods of apnea During the examination the baby stopped breathing, became cyanotic and the extremities became rigid. Carbon dioxide and oxygen were administered and immediately restored the respirations The child was extremely pale and the skin was loose and had poor turgor The head appeared normal and both fontanelles were open The anterior fontanelle was tense and bulged slightly The lymph nodes were not palpable The conjunctivae were intensely yellow Several ecchymotic spots were noted on the hard palate Examination of the ears, nose, lungs and heart revealed no abnormalities The liver was palpable two fingers' breadth below the right costal margin, but the spleen was not palpable. There were ecchymoses on the inner aspect of the left ankle and on the right arm about the elbow The neurologic examination showed hyperactive reflexes but no signs of meningeal irritation.

*Laboratory findings* The urine examined on admission had a deep yellow color but all other determinations were negative The red blood cell count on admission was 3.04 million, the white cell count was 60,600 The differential count showed 2 juveniles, 19 stabs, 42 segmental, 37 lymphocytes and 10 monocytes. Many nucleated red blood cells and basophilic staining red blood cells were noted in the smear The tuberculin test was negative. A spinal puncture, performed the day of admission, revealed xanthochromic fluid but the Pandy test was negative The bleeding time was 1 minute and the clotting time  $1\frac{1}{2}$  minutes A fragility test was performed and was normal

*Course in the hospital* The clinical diagnoses at that time were icterus gravis with secondary anemia, alkalosis and dehydration and a possible septicemia. The neurological consultant made an additional diagnosis of internal hydrocephalus, probably due to hemorrhage or some congenital anomaly. It was stated that the child would be quiet for 15 to 30 minutes and then suddenly cry loud and forcefully for 1 to 2 minutes. A considerable amount of mucus was found in the throat. Sixty cc of whole blood intravenously and 400 cc of Ringer's solution were given subcutaneously. The temperature was slightly elevated the first three days in the hospital. It was noted on the third hospital day that the anterior fontanelle was full and tense. A cisternal puncture was done and spinal fluid was removed under greatly increased pressure. The fluid was blood-tinged but the blood was believed to be due to a small hemorrhage during the procedure. Microscopic examination disclosed many red blood cells, half of which were crenated. No fluid was found in the epidural space. The fontanelle was perceptibly softer and less full following the puncture. On the fourth day a left ventricular puncture was performed and about 12 cc of homogeneously blood-tinged fluid was withdrawn under slightly increased pressure. At this time it was noted that the child had a ptosis of the left eyelid and the right pupil was dilated. The respirations remained the same. There was an apparent improvement in the child's condition during the next few days and he was discharged from the hospital with instructions to return to the Children's Hospital once a month.

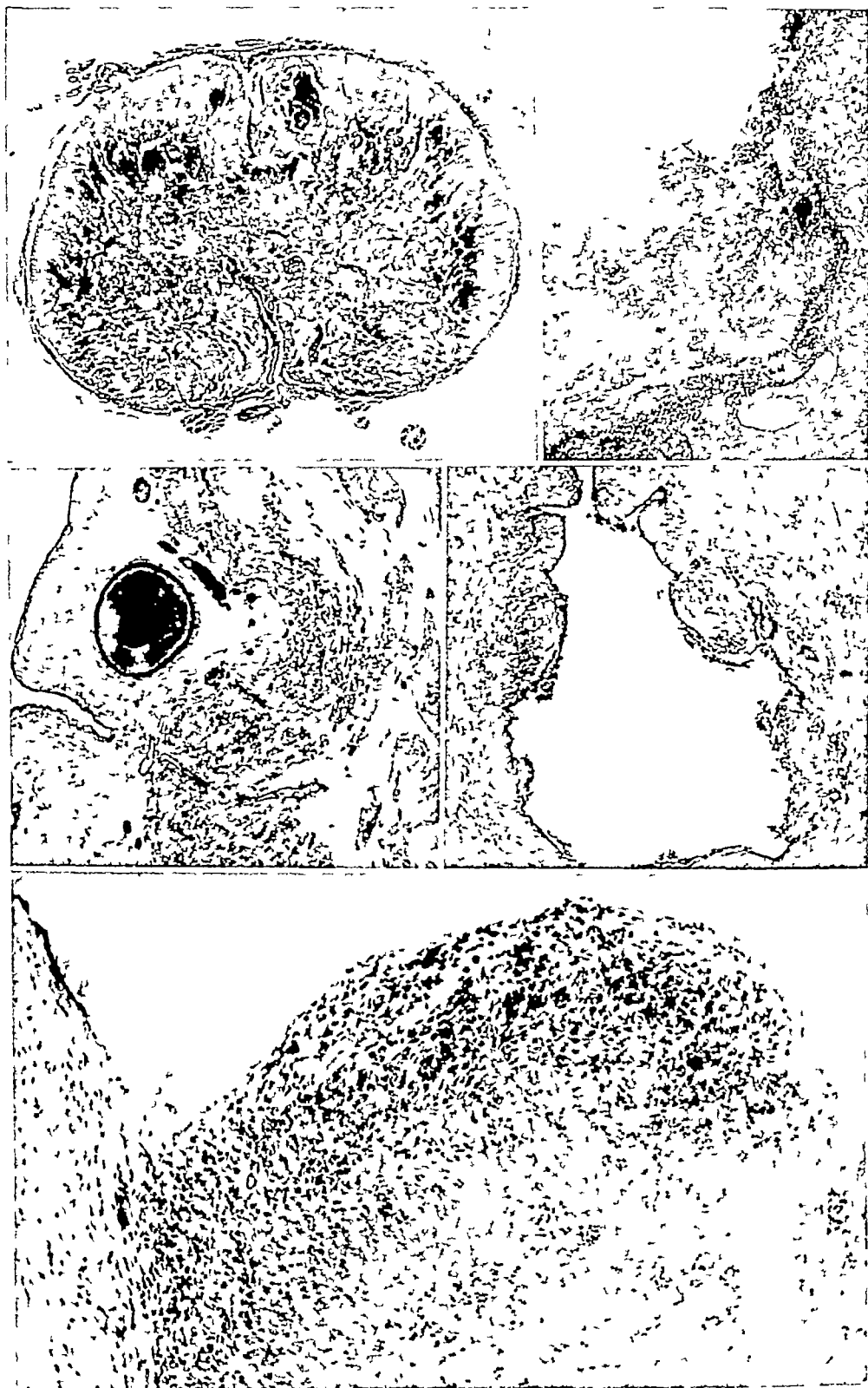
*Second hospital admission* The child was readmitted on December 22, 1934 with the complaint of having cried continuously for four days. Peculiar movements of the arms and legs had been noticed for four days and the child had a slightly elevated temperature the day before entry. It was learned that after being discharged from the hospital the child was well and without signs or symptoms for four or five days. Following this initial period he began to cry a great deal but after an increase in his formula he cried much less. On the eighth day after his discharge he began having unusual attacks of jerking movements of his arms and legs. The attacks increased in frequency until they occurred almost continuously. He had cried continuously for the four days before entry and the day before entry had a slight generalized convulsion. The evening of admission he became cyanotic. In spite of the convulsive movements and manifest discomfort the child had taken his feedings well until the day of entry. However, he had a mild upper respiratory infection for three days before his admission.

*Physical examination* At the time of entry the infant was restless, cried much and appeared acutely ill. The temperature was  $40^{\circ}\text{C}$ , the pulse rate was 130 per minute and the respirations 75 per minute. The child was cyanotic and had repeated clonic convulsive movements of his upper extremities. He held himself extremely rigid and at times assumed an opisthotonic position. His neck was stiff but at times it could be flexed. The convulsive seizures were usually characterized by a generalized hypertonicity that was most marked in the upper extremities where the forearms were flexed on the arms and the fists tightly clenched. Rapid clonic movements were also noted to accompany the seizures in the upper extremities but were never observed in the lower extremities. The

anterior fontanelle was depressed and there was slight overriding of the parietal bones. The posterior fontanelle was also open and depressed. There was a partial ptosis of the upper lid of the right eye, but the lid could be raised voluntarily by the patient. The conjunctivae, corneae and sclerae were clear. The pupils were unequal, the left being slightly larger than the right. The left pupil reacted slowly and with small amplitude to light. The pupil of the right eye reacted normally. The external ocular movements were normal. Examination of the nasopharynx revealed no pathologic change. There was no mastoid swelling or tenderness. The tympanic membranes were seen with difficulty. The light reflex was not obtained on either side and there was a slight redness and bulging of the right tympanic membrane but nothing unusual on the left. The chest was symmetrical and the superficial veins were prominent over the anterior aspect. The respiratory excursions were shallow, variable in depth and of the Cheyne-Stokes type. The respiratory rate was from 70 to 80 per minute. The chest was resonant to percussion and the breath sounds were vesicular. Examination of the heart showed no increase in size and the rate and rhythm were normal. The pulse rate was 130 per minute and of good quality. The abdomen was flat and soft. The spleen was easily palpable one finger's breadth below the costal margin. The liver was also palpable 2 to 3 fingers' breadth below the costal margin. The genitalia, extremities and all the reflexes were normal. No pathologic reflexes were elicited.

*Laboratory data* Laboratory studies done at the time of the second admission revealed the urine normal, the hemoglobin 82 per cent, a red blood cell count of 4.2 million per cubic millimeter and the white blood cell count was 19,200 per cubic millimeter. The differential blood count was normal except for an occasional nucleated red blood cell. A lumbar puncture revealed xanthochromic fluid with 18 cells per cubic millimeter. All of the cells were lymphocytes. The Pandy reaction was one plus. The clinical diagnoses were 1) possible tetany, 2) otitis media and 3) convulsions possibly due to birth injury. A consultant from Otorhinolaryngology made a diagnosis of acute purulent mastoiditis and on January 5, 1935 a bilateral mastoidectomy was performed. Following the operation the patient continued to have an elevated temperature and lost more weight in spite of the administration of subcutaneous fluids. He vomited repeatedly and copiously. The last two days before death he was completely blind. Respirations became more rapid and the temperature rose to 41°C. Despite supportive measures the patient expired January 25, 1935, on the thirty-fourth hospital day.

*Autopsy* Washington University Autopsy #6011 was performed seven hours after death. The body weighed 12.5 kilograms and measured 56 cm. in length. The fontanelles were not closed and there was unusual tension noted when the fontanelle was palpated. The eyes were sunken and the skin and sclerae had a pale yellow icteric color. There was a 1 cm. incision behind each ear containing a small rubber drain from which purulent material exuded. The spleen and liver weighed 17 and 80 grams respectively. No significant gross pathologic change was found in the liver, spleen, gastrointestinal tract or the kidneys. The visceral



FIGS 1-5



and parietal pleurae were smooth, bright and glistening. The right pleural cavity contained approximately 30 cc of light amber fluid. Small foci of atelectasis, characterized by a slight depression of the lung parenchyma and purplish discoloration of the pleura, were found in the posterior aspects of both lungs. When the calvarium was removed a moderate amount of clotted blood without evidence of organization was noted on the left side. There was marked thinning of the cerebral cortex and sections through the hemispheres revealed a marked dilatation of the entire ventricular system.

*Microscopic examination.* A section of lung disclosed a moderate amount of edema of the interlobular septa and peribronchial tissues. In some parts of the section the alveoli were partially collapsed, their walls appeared slightly thickened and there were scattered lymphocytes and plasma cells. Dark brown masses of inspissated bile were noted in and between the liver cells. One section taken from the spleen disclosed many large macrophages in the red pulp filled with a moderate amount of golden brown pigment.

A section of brain taken from the left cerebral hemisphere revealed complete destruction of the normal cyto-architectonics of the cortex with loss of all of the nerve cells. The normal cellular arrangement of the nervous tissue was loose and the tissue was packed with large vacuolated gutter cells, scattered lymphocytes and plasma cells. This type of pathologic change was particularly marked in the cortical gray matter, there being less infiltration in the subjacent white matter. Several focal areas of a granulomatous type of reaction were observed. Toxoplasmas were found in and around the granulomatous areas occurring in clumps surrounded by a membrane giving the appearance of a "cyst wall" (Fig 13), and also occurring singly in the brain substance (Figs 10, 11, 12, 14). The organisms had a definite deeply stained nucleus and a pale

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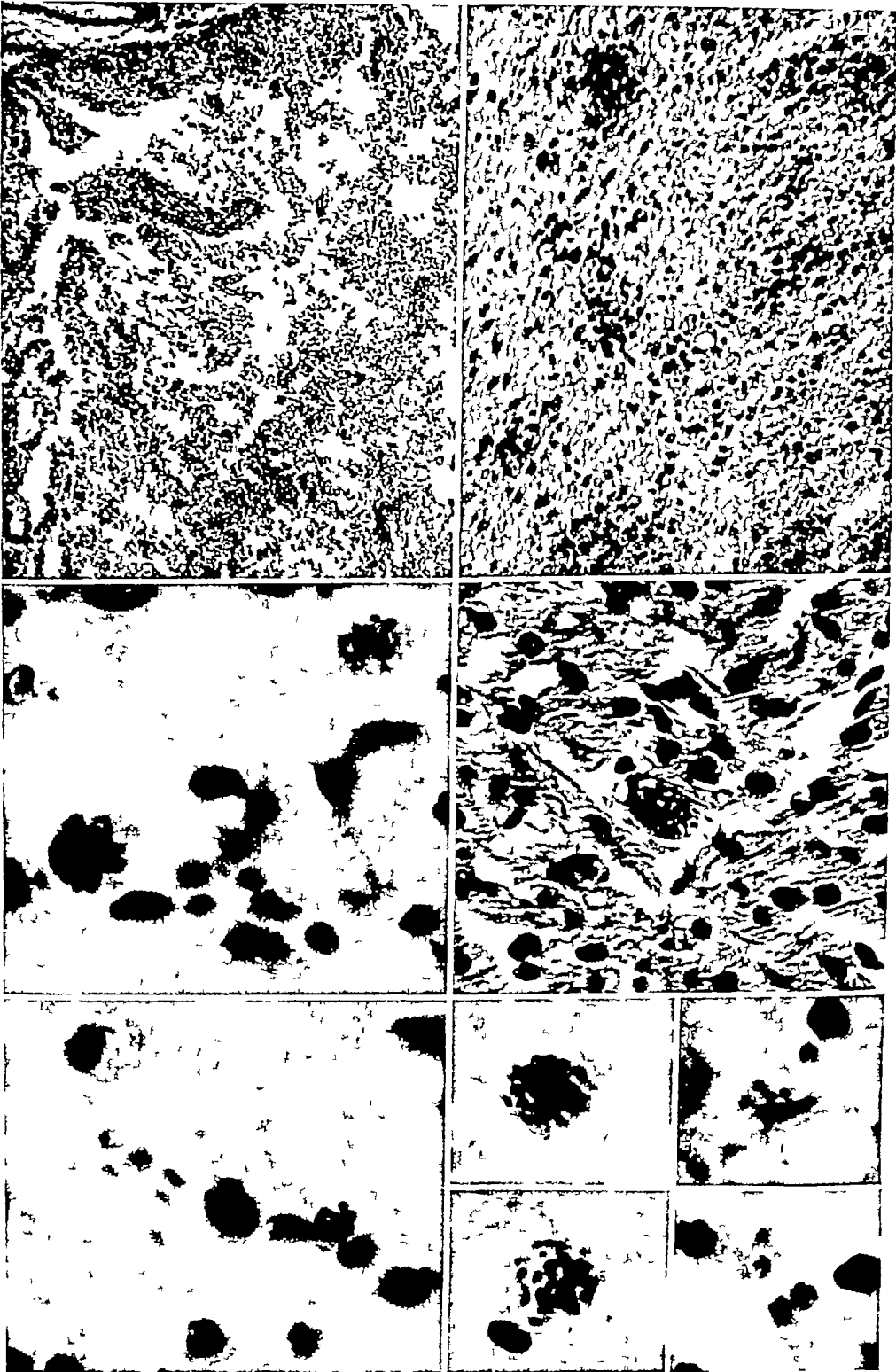
FIG 1 Case No 4. Cross section of the spinal cord from a lower lumbar segment showing extensive myelomalacia. The gray matter and large amounts of the adjacent white matter have been largely destroyed. Hematoxylin and eosin stain.  $\times 50$ .

FIG 2 Case No 5. Section from a small ulcer in the lateral ventricle. There is a caseous type of necrosis destroying the ependyma and subependymal tissues. The caseation is surrounded by a broad zone of granulation tissue. The deep staining of the granulation tissue is partly due to finely granular deposits of calcium. Hematoxylin and eosin stain.  $\times 50$ .

FIG 3 Case No 3. This section from the left occipital lobe shows complete destruction of the underlying cortical architecture with the formation of cysts. The cysts are multiloculated and the walls are composed of dense accumulations of glial cells and fibers. The molecular layer of the cortex and the pia glial membrane have been distorted as a result of the destruction of the underlying nervous tissue. The depth of the subarachnoid space has been increased and there are scattered lymphocytes and plasma cells present. Hematoxylin and eosin stain.  $\times 135$ .

FIG 4 Case No 4. Cerebral aqueduct showing reactive ependymitis. The ependymal cells are displaced and in one instance destroyed by oval masses of glial tissue formed beneath the ependymal covering. Scattered glial nodules are seen in the adjacent tissues and in two instances within the subependymal masses of glial tissue. Hematoxylin and eosin stain.  $\times 135$ .

FIG 5 Case No 5. This section was taken from the largest ulcer seen in the ventricle. The intact ependyma is seen in the upper left hand side of the photograph. The ulcer was formed from a large granulomatous mass of tissue projecting from the wall of the ventricle with caseous necrosis in the central part. One edge of the raised crater is seen in the upper central part of this figure. Note the central mass of caseous necrosis. The irregular small masses of deeply staining material are masses of blue staining calcium. Hematoxylin and eosin stain.  $\times 300$ .



Figs 6-14

but well defined cytoplasm. In all of the granulomatous areas many of the pathologic cells contained fine granules of blue-staining calcium in their cytoplasm. In some areas the calcification of individual cells was so advanced that as a result broad bands of calcific material were formed. Several of such areas of calcification were observed. The spaces of Virchow-Robin and the sub-arachnoid space were filled with lymphocytes, plasma cells and macrophages.

The middle ears with a large part of temporal bone were sectioned following adequate decalcification. Examination of a section taken from the left ear disclosed a large amount of highly vascular granulation tissue in the operative wound that was infiltrated with a large number of polymorphonuclear leucocytes. There was liquefaction of the marrow with a marked destruction of the bony trabeculae in the mastoid part of the temporal bone that remained. Examination of sections taken from the right ear disclosed essentially the same type of pathologic change as was noted in the left ear. Small intra- and extracellular microorganisms identifiable as *Toxoplasma* were seen in the sections from the left middle ear.

*Pathologic diagnoses* The anatomic diagnoses were toxoplasmic encephalomyelitis, internal hydrocephalus, toxoplasmic otitis media, bilateral, icterus, generalized, inspissated bile in the liver cells, hemorrhage between the dura mater and calvarium, focal atelectasis of the lungs and slight interstitial pneumonia.

### Summary of case

A seventeen-day-old infant who had been jaundiced since birth was admitted to the hospital because of vomiting. A diagnosis of icterus gravis and internal

FIG 6 Case No 4. Section from the anterior column of the spinal cord. The anterior spinal artery is shown in the upper left hand side of the field. Note the extensive myelomalacia with loss of all of the architectural pattern of the tissue. The cells observed are largely gutter cells. Hematoxylin and eosin stain.  $\times 150$

FIG 7 Case No 3. Focal granulomatous lesions in the white matter of the cerebrum. The cells are chiefly lymphocytes, plasma cells and macrophages. Hematoxylin and eosin stain.  $\times 500$

FIG 8 Case No 5. Two large aggregates of *Toxoplasma* organisms are seen in two corners of the photograph. No cyst wall can be identified. Two groups of two organisms each are seen in the lower middle part of the field. Hematoxylin and eosin stain.  $\times 1100$

FIG 9 Case No 1. A myocardial fiber seen in the center of the field is filled with a large number of *Toxoplasmas*. Note the complete absence of reaction in the tissue surrounding the parasitized fiber. Hematoxylin and eosin stain.  $\times 700$

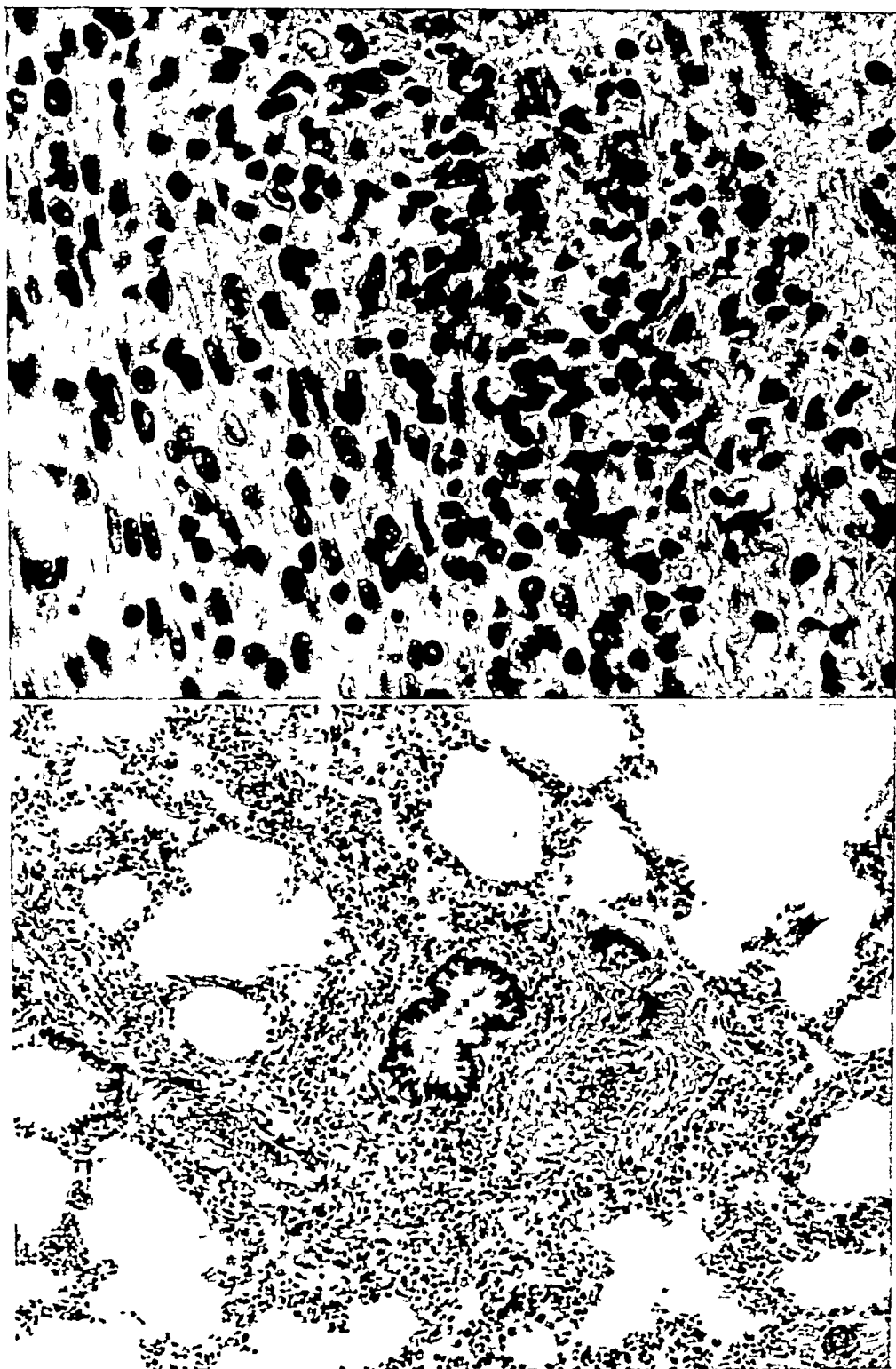
FIG 10 Case No 2. Six isolated *Toxoplasmas* near the nucleus of a macrophage. Note the crescentic form of the cytoplasm and the slightly oval nucleus. A small cluster is seen to the right of the macrophage. Hematoxylin and eosin stain.  $\times 1100$

FIG 11 Case No 2. A large aggregate of *Toxoplasmas*, many exhibiting crescentic form. The structure surrounding the organisms is probably not a capsule or the wall of a pseudocyst but an artefact from fixation, since similar outlined areas can be seen. Compare with Fig 13. Hematoxylin and eosin stain.  $\times 1100$

FIG 12 Case No 2. A group of five *Toxoplasmas* between the nuclei of two cells. The organism at the extreme left has the cytoplasm clearly defined and a clearly shown oval nucleus. Hematoxylin and eosin stain.  $\times 1100$

FIG 13 Case No 2. A large mass of *Toxoplasmas* contained in a pseudocyst. The cyst wall is clearly defined. Hematoxylin and eosin stain.  $\times 1100$

FIG 14 Case No 2. Two groups of *Toxoplasmas*. The group occupying the upper left hand position has one organism in focus showing its extreme crescentic form. Hematoxylin and eosin stain.  $\times 1100$



Figs 15-16

hydrocephalus was made and the infant was given supportive treatment. He was discharged from the hospital slightly improved.

He was readmitted to the hospital twenty three days later with convulsive seizures and partial ptosis of the right eye. The course was progressively worse and despite a bilateral antrotomy the patient died on the thirty-fourth hospital day. At autopsy internal hydrocephalus, encephalomyelitis, bilateral otitis media and interstitial pneumonia were the principal lesions. Toxoplasmas were identified in the sections of brain and the left middle ear.

### *Comment*

The presence of jaundice since birth and the diagnosis of internal hydrocephalus 17 days later is presumptive evidence that this represents an infection acquired in utero. The pathologic changes support this assumption. The observation that the child became totally blind is interesting although there are not sufficient clinical or pathologic studies to merit any conclusions. The frequency with which *Toxoplasma* produces changes in the choroid and retina is well known and it is probable that such was the case in this instance. No ophthalmoscopic examinations were performed and the eyes were not examined at the time of autopsy. The extensive calcific deposits in the brain would undoubtedly have been demonstrated if roentgenograms of the skull had been made.

This is the first reported case in which parasites have been identified within the mastoid process. It is probable that an intercurrent bacterial infection was also present because of the large amounts of purulent material observed clinically in the ear and from the type of response present in the mastoid process. The cellular reaction consisted almost entirely of polymorphonuclear leucocytes. The method of spread to the mastoid process is not clear but it is unlikely that the ear served as a portal of entry.

*Case III* N L E (Children's Hospital, St. Louis, Mo., #L-687), a white female infant two months of age was admitted to the St. Louis Children's Hospital April 3, 1935 and died April 8, 1935.

*Chief complaints* Those given by the child's parents were repeated attacks of generalized convulsions of two weeks' duration and diarrhea for the past six days.

*Family history* The child's mother and father were each 24 years of age and were living and well. There was a sister three and one-half years of age who was in good health. There had been only two pregnancies and there was no history of tuberculosis or of other chronic illnesses in the family.

*Past history* The patient was born at home following a reportedly normal term delivery and weighed seven and one-half pounds at birth. She cried spontaneously and was breast fed for one week followed by supplementary

FIG 15 Case No 4 Focal necrosis of myocardial fibers. The cells infiltrating the lesion are lymphocytes, macrophages and occasionally a polymorphonuclear leucocyte. Hematoxylin and eosin stain.  $\times 570$ .

FIG 16 Case No 4 Interstitial inflammation of tissue surrounding a small bronchus and in the pulmonary alveoli. The alveolar walls are increased in thickness and infiltrated with plasma cells and lymphocytes. Hematoxylin and eosin stain.  $\times 150$ .

feedings of cow's milk, water and Kao in equal parts. After one month there was no breast milk and she was given canned milk until her illness. There was a history of constipation and occasional attacks of vomiting. History of respiratory infections or of any other illness was not obtained. At one month she weighed ten pounds but had not been weighed since.

*Present illness* Two weeks before entry to the hospital the infant had several generalized convulsions. These were described as lasting for several minutes with the convulsive movements involving the entire body, on several occasions there was retraction of the head and unusual movements of the eyes and frothy material appeared in the mouth. There had been no vomiting or cyanosis and the rectal temperature, taken at home was 101.5°F. Because of these symptoms the patient was admitted to the St. Mary's Hospital in East St. Louis on March 21, 1935. A lumbar puncture was performed on admission and bloody fluid was obtained. After an initial period of one day in which there were involuntary movements of the eyes, the patient's condition was notably improved. However, she was extremely irritable to all external stimuli and would jump at the slightest noise. Her general condition improved and she was discharged from the hospital on March 26, 1935.

At home the infant appeared well for several days but soon began vomiting after meals. The vomiting appeared about fifteen minutes after each feeding and was described as forceful and of the projectile type. There was also some diarrhea and the stools contained mucus and bright red blood. The day before admission to the St. Louis Children's Hospital she became much worse, refused food and water, and cried continuously. She was again taken to the St. Mary's Hospital where parenteral fluids were administered which partially alleviated the acute symptoms. It was noted at that time, however, that the eyes were fixed and breathing was fast and labored. The patient was referred to the St. Louis Children's Hospital for treatment.

*Physical examination* The infant was well developed and was lying listlessly in bed with sunken eyes and fixed pupils. The skin was pale, breathing was rapid and deep with accessory muscles of respiration being used. The turgor of the skin was good and there was no skin rash, but the scalp was reddened in the left temporal and occipital regions. The anterior fontanelle was open and did not bulge, but pulsations could be felt. The eyes were sunken and the corneas and conjunctivae were dry and did not respond to stimulation. The left tympanic membrane was reddened and there was a mucopurulent discharge from the nose. Although the mouth was held half open, it was extremely difficult to open farther. The posterior pharynx was reddened and the neck was slightly stiffened. There were no congenital abnormalities. Coarse rhonchi were heard throughout both lung fields and medium sized rales were heard posteriorly on the right side. The heart sounds were described as of fair quality and the pulse rate was 120 per minute. It was difficult to examine adequately the abdomen because of fluid in the subcutaneous tissues. All of the extremities were flaccid but the reflexes were all present and were equal and active. A slight rigidity was noted in the neck but the Kernig and Brudzinski signs could not be elicited.

*Laboratory findings* Laboratory studies made at the time of admission revealed nothing remarkable in the urine, the hemoglobin was 82 per cent, the red blood cell count was 4.26 million and the white cell count was 27,400 per cubic millimeter of blood. The differential blood count revealed 7 juveniles, 30 stabs, 45 segmented forms, 15 lymphocytes and 3 monocytes. The carbon dioxide combining power of the blood was 19 volumes per cent. The tuberculin and Kline tests were negative. A lumbar puncture was performed on the day after admission and revealed clear spinal fluid with 31 cells per cubic millimeter. All of the cells were determined to be lymphocytes. The Pandy reaction was 3 plus and the spinal sugar was 73 milligrams per cent.

*Hospital course* At that time the following diagnoses were considered: diarrhea with dehydration, acidosis and hiccoughs, tetanus, meningitis and possibly birth injury. On the day following admission a generalized rigidity was noted with the lower extremities markedly more spastic than the upper extremities. The rigidity of the neck remained the same and the anterior fontanelle bulged slightly. There was some rigidity of the abdominal muscles and the spleen and liver were palpable. The reflexes were all hyperactive and the clinical impression at that time was that a spastic paraplegia of an undetermined cause had developed. On the second hospital day a slight opisthotonos was noted and the extremities were held rigid. The jaw remained stiff and was difficult to force open. In view of the opisthotonos and muscle rigidity a diagnosis of tetanus was regarded as a strong possibility and 20,000 units of tetanus antitoxin were given by the intramuscular route. Three days later on April 8 her condition became notably worse and was characterized by rapid shallow respirations with expiratory grunts. The lungs were filled with medium and fine rales. A blood calcium determination showed 9 milligrams per cent with a blood phosphorus of 5 milligrams per cent. The nonprotein nitrogen was 52 milligrams per cent and the total proteins were 5.6 milligrams per cent. Stool cultures were negative for organisms of the typhoid dysentery groups and a stomach culture revealed only a few colonies of *E. coli*. The patient's course was rapidly downhill and she died on April 8, five days after her admission to the St. Louis Children's Hospital.

*Autopsy* Washington University Autopsy #6094. The postmortem examination was performed five and one-half hours after death and was restricted to examination of the head. The body was that of a well nourished and fairly well developed two-months-old female infant. The abdomen was slightly distended and tympanitic. There was nothing unusual noted in the size and shape of the head. The anterior fontanelle was open. Sections through the brain revealed marked dilatation and enlargement of the temporal and occipital horns of the lateral ventricles, but the anterior horns were normal. The temporal and occipital horns of the ventricles were ill defined because of the extensive softening of the surrounding brain tissue. In the occipital and temporal lobes several cystic cavities were observed which were believed to be continuous with the lateral ventricles surrounding the cavities and involving both occipital and temporal lobes. There was extensive encephalomalacia of the brain tissue in

these areas. Sections taken through the remaining parts of the brain showed no further gross pathologic change.

*Microscopic examination* A section taken from the left temporal lobe disclosed scattered lymphocytes and plasma cells in the subarachnoid space. There was a complete loss of the nerve cells of the underlying cortex. The cortex was infiltrated with many finely vacuolated macrophages. The infiltration and alteration of the brain tissue was less marked in the underlying white matter than in the cortex. Focal granulomatous lesions containing plasma cells, lymphocytes and, in certain instances, cells resembling epithelioid cells were noted in the cortex (Fig 7). In these areas of granulomatous reaction many of the macrophages contained fine basophilic-staining blue granules of calcium. Small microorganisms with a small nucleus and an ill defined cytoplasm were found in the granulomatous areas previously described. The organisms were in clusters and lying free between the cells. A section taken from the occipital lobe in the region of one of the cavities noted in the gross examination showed the same type of massive destruction of nervous tissue with infiltrations of gutter cells and scattered focal areas of granulomatous reaction which was similar to that noted in the section taken from the left temporal lobe. In part of this section, however, in the region of the large cavity there were many smaller cavities, in most instances communicating with the large cavity. All of the cavities had a smooth lining composed of dense accumulations of glial fibrils surrounded by a broad zone of gliosis. In many areas there was complete destruction of the cortex, there being only a thin lining of glial tissue at the pial membrane with scattered islands of dense glial tissue in the larger cavities (Fig 3). There were many scattered foci of deep blue-staining granular calcific material throughout the section. Other sections taken from the occipital and temporal lobes showed essentially the same type of pathologic change as has been described above.

The pathologic diagnoses were toxoplasmic encephalomyelitis, with cyst formation in the occipital and temporal lobes, and internal hydrocephalus.

#### *Summary of case*

A white female infant, delivered at full term, became ill at six weeks of age and developed severe generalized convulsions, diarrhea and signs of spinal cord involvement. The course of the disease was rapid, and terminally signs of respiratory infection became apparent. Autopsy revealed internal hydrocephalus and a widely disseminated encephalomyelitis with foci of necrosis and numerous milary granulomatous lesions. Many of the lesions had undergone cystic degeneration while others, especially in the cerebral cortex, were calcified. Microorganisms identified as *Toxoplasma* were found in the granulomatous foci. The autopsy was limited to the head, and the eyes were not examined.

#### *Comment*

Although signs and symptoms did not develop until six weeks after birth the rapid clinical course suggests that the disease may have been active before this period. The extensive calcific deposits in the brain and the small and large



cysts are pathologic changes that take longer to produce than the two week period when the patient had definite clinical symptoms. It seems reasonable to conclude from the nature of the pathologic changes that the infection was acquired in utero and was apparently sufficiently well localized to cause no notable signs or symptoms. At the age of six weeks the process spread and involved the entire central nervous system producing the widespread encephalitis with milary granulomas. The original or primary lesions consisted of focal calcification and cystic degeneration. It is unfortunate that the autopsy was limited to the head and that the systemic manifestations of the disease could not be studied.

*Case IV* G.F. (Children's Hospital, St. Louis, Mo., #M-2280) a seven-weeks-old white male infant was admitted to the St. Louis Children's Hospital on December 9, 1936 and died December 24, 1936.

*Chief complaints* The parents stated that the child had failed to gain weight since birth and that six days prior to admission he had developed an upper respiratory infection with a profuse watery type of nasal discharge, irregular respirations and cough.

*Family history* The infant's father was a clothing merchant and the mother had no occupation except her duties as a housewife. Both were in good health. There was one brother and two sisters living and well. The three children had developed normally since birth and the delivery in each instance was regarded as normal. There was no history of chronic illnesses in the family.

*Present illness* At birth the child weighed 5½ pounds and the delivery was considered normal, although the child was about two weeks premature and there was some difficulty in getting him to breathe at birth. No signs or symptoms indicating central nervous system disease were noted in the child and the mother was apparently well and healthy. The child was fed exclusively from the mother's breast for about ten days followed by supplemental feedings after each breast feeding of a Pet milk and Karo formula. Although it was stated that the patient took the feedings well, he did not gain in weight. Two weeks before entry to the hospital he had an attack of diarrhea with four or five greenish-yellow, blood-streaked stools per day. After one week the diarrhea ceased but blood-streaked stools had been noted at intervals. The patient, weighing four pounds and nine ounces at admission, had lost two pounds in the past two weeks. The temperature had always been subnormal, the lowest reading being 93°F. The infant had not received orange juice or cod liver oil and had not suffered from any communicable disease. Because of an upper respiratory infection three days before admission, the patient was brought to the St. Louis Children's Hospital where nose drops were prescribed and the formula altered. Although there had been a purulent discharge from the right eye since birth it had recently cleared up.

*Physical examination* Examination on entry to the hospital revealed a thin, malnourished seven weeks old white male infant weighing 4 pounds 9½ ounces. The skin was loose and dry and had poor turgor. The fontanelles were open and there was a slight bulging of the anterior fontanelle with a wide suture line.

The circumference of the head was  $13\frac{1}{2}$  inches. The pupils were equal and reacted to light equally. A small amount of crusted dry exudate was noted around the right eye and in the external nares. The ears, mouth and gums were normal. The chest was thin but symmetrical and was resonant on percussion with only a few scattered moist rales heard over both lung fields. The heart sounds were clear and the rate and rhythm were normal. The liver was palpable below the right costal margin but the spleen and kidneys were not felt. The extremities were thin and the joints were prominent and freely movable. The reflexes were physiological.

*Laboratory findings* On admission examination of the urine was negative. The hemoglobin was 75 per cent, the red blood cell count was 4,230 million and the white blood cell count was 11,200 with a normal number of platelets. The differential count disclosed 3 juvenile forms, 21 stabs, 39 segmented forms, 34 lymphocytes and 3 monocytes. The red cells appeared normal and the bleeding time was 9 minutes and the clotting time 3 minutes. The tuberculin and Kline tests were negative. A lumbar puncture performed the day after admission revealed 140 red blood cells and 37 white blood cells, 3 polymorphonuclear leucocytes and 34 lymphocytes per cubic millimeter of spinal fluid. The Pandy test was negative and smears and cultures of the fluid showed no organisms. Examination of the stool was negative except for a weak guaiac reaction.

*Course in hospital* The patient's temperature varied from  $38.4^{\circ}\text{C}$  to  $36^{\circ}\text{C}$ . For the first few days the temperature elevation was noted in the afternoons and in the evenings.

On the second hospital day another lumbar puncture was done because the anterior fontanelle was still bulging, and 6 cc of bloody fluid was removed. At that time 50 cc of 10 per cent glucose was given intravenously and 75 cc of Ringer's solution subcutaneously. The bleeding time was 6 minutes. The following day the anterior fontanelle was noted to bulge more than previously and another lumbar puncture was performed and 6 cc of slightly bloody fluid was removed. This was all the fluid that could be obtained and it was noted that the removal of the spinal fluid did not cause a decrease in the bulging of the anterior fontanelle. A transfusion of 50 cc of citrated blood was then given. The circumference of the head at that time was  $13\frac{1}{2}$  inches. On the sixth hospital day a cisternal puncture was performed but it was possible to remove only 5 cc of slightly bloody fluid. At the same time the right lateral ventricle was tapped and 45 cc of fluid removed. Examination of the fluid disclosed 84 cells per cubic millimeter without acid but only 18 cells with acid. The Pandy test was 3 plus. Before the ventricular puncture the circumference of the head was 14 inches but no change was noted after the puncture. However, the tension of the fontanelle was relieved by the removal of the fluid. On December 17, 1936 the circumference of the head had increased again, the measurement being  $14\frac{1}{4}$  inches. Three days later on December 20 a left ventricular puncture was performed and 38 cc of markedly xanthochromic fluid was removed. The right ventricle was also tapped but only 15 cc of xanthochromic fluid was removed that was apparently not under increased pressure. At this time 300

cc of lactate Ringer's solution was given. On December 17 protuberance of the lower abdomen was noted which was believed to be the urinary bladder, and it was believed at that time that the child had a paralysis of the bladder. An unsuccessful attempt was made to relieve the urinary retention by catheter. Continuous pressure on the bladder expelled 15 to 20 cc of urine. On the following day there was complete paralysis of the right side of the body. During the next few days the child became extremely listless and reacted poorly to even strong stimuli. On December 24 there was noted a marked decrease in the tone of the muscles of both upper extremities. The arms were flaccid and the fists were clenched, the deep reflexes were exaggerated in the upper extremities. The abdomen was greatly distended and there was incontinence of both the bladder and the rectum. The patient did not respond to painful stimuli below the level of the costal margins. The lower extremities were extremely thin and there was almost complete atrophy of the muscles. There was no reflex activity on either side with the exception of a faint contraction of the hamstring group of muscles following the stimulation of the patellar tendon. The patient died following a few hours of rapid and shallow respirations.

The clinical diagnoses were spastic paralysis of the upper extremities, internal hydrocephalus, and a transverse lesion of the spinal cord, probably the result of a hemorrhage into the cord.

*Autopsy* Washington University Autopsy #6728. The body was that of a fairly well developed but poorly nourished nine weeks old white male infant weighing 2140 grams and measuring 57 cm in length. The anterior fontanelle was not closed and a slight prominence of the upper part of the head was noted. Examination of the lungs revealed atelectasis of the entire right upper lobe and a small part of the right middle and lower lobes. The atelectatic areas were a dark purplish color and slightly depressed as compared to the surrounding lung tissue. The spleen and liver weighed 20 and 50 grams respectively and nothing remarkable was noted when these organs were sectioned. Small focal hemorrhages were seen in the mucosa of the urinary bladder. The calvarium was removed without difficulty. Because of the unusual softness of the brain tissue the brain was torn in several places when it was removed. Large amounts of clear, colorless spinal fluid escaped from the ventricles when torn during removal from the skull. External examination of the brain disclosed the cerebral hemispheres unusually large with the cerebral convolutions small and flattened. The brain was sectioned following formaldehyde fixation. The sectioning revealed several areas of encephalomalacia in the white matter of the left cerebral hemispheres, the largest measuring  $2 \times 1 \times 1$  cm and lying in the medial part of the inferior part of the left temporal lobe. Two smaller areas, each approximately  $2 \times 1$  cm, were described in the left frontoparietal region near the central fissure. Surrounding the smaller softened areas there was a conspicuous yellow discoloration of the brain tissue. The lateral and third ventricles were markedly dilated and small deposits of grayish-yellow material were seen on the surfaces of the ventricles. The aqueduct of Sylvius was patent.

The spinal cord when removed appeared normal but on sectioning there were

found several areas of softening in the lumbosacral region similar to those noted in the cerebral hemispheres

*Microscopic examination* In one section taken from the heart there were multiple small foci of lymphocytes and macrophages scattered diffusely through the myocardium. In some of these areas there was disruption and necrosis of several of the muscle fibers (Fig 15). No parasites were identified in any of the lesions. A section of lung disclosed a small area of atelectasis. In other areas of the section the alveoli contained polymorphonuclear leucocytes, fibrin and vacuolated macrophages. Many of the alveolar walls were thickened and infiltrated with plasma cells and lymphocytes (Fig 16). A section of spleen revealed several small focal areas of necrosis in the red pulp. There was some infiltration of polymorphonuclear leucocytes and hemorrhage into these areas but no microorganisms could be found. The type of reaction did not suggest a specific type of inflammation. Sections of the kidneys showed diffuse interstitial type of infiltration with lymphocytes. No organisms could be found.

A histologic examination of the posterior part of the medulla oblongata revealed two areas of reactive ependymitis on the surface of the fourth ventricle. In these areas the ependymal cells were replaced by a mass of glial tissue bulging into the cavity of the ventricle. The glial tissue was remarkably vascular and for the most part composed of large numbers of fibrillary astrocytes with a few gitter cells interspersed. Scattered gitter cells and lymphocytes were noted in the subarachnoid space in two areas. A section taken through the mesencephalon at the level of the superior colliculus and the base of the cerebral peduncles revealed large areas of softening on the right side that involved the substantia nigra, the medial lemniscus and the inferior part of the nucleus of the inferior colliculus. In the involved areas there was complete necrosis of the tissues and replacement by a light eosinophilic staining coagulum containing many macrophages, an occasional lymphocyte and innumerable pyknotic nuclei. Scattered throughout all parts of this section, but particularly numerous around the area of encephalomalacia, were small focal glial nodules. Each nodule was composed of approximately 50 to 60 cells. Fibrillary astrocytes, macrophages and occasionally plasma cells were identified in the nodules. Several of these glial nodules were seen in the region of the cerebral aqueduct. There was a reactive ependymitis present, the nodules projecting into the lumen of the aqueduct (Fig 4). In a section taken from the left temporal lobe, there were large cystic cavities containing scattered gitter cells and many small islands of dense glial tissue. The walls of the cavity and the islands of glial tissue were composed of fibrous astrocytes with heavy fibrillary processes. Small collections of finely granular blue-staining calcium with minimal cellular reaction were scattered in this tissue showing the advanced gliosis. It appeared in certain instances that the granules of calcium took the exact form and outline of large macrophages. No glial nodules were seen in this section. A second section taken from the temporal lobe showing the temporal horn of the ventricle and a tuft of choroid plexus revealed marked destruction of the white matter beneath the ventricle in the region of the attached choroid plexus. The tissue showing the pathologic

change was infiltrated with large numbers of gitter cells and astrocytes. One large area of granulomatous reaction with many of the cells containing fine blue-staining granules of calcium was seen beneath the surface of the ventricle. In some parts of this granulomatous area there was necrosis of the cells resembling caseation. Many small glial nodules were seen throughout the section and they were particularly numerous in the region of the previously mentioned large areas of granulomatous reaction. The connective tissue stroma of the attached choroid plexus contained scattered plasma cells and a few macrophages.

A section taken through the basal ganglia disclosed several large areas of encephalomalacia with complete destruction of the normal cyto-architecture. The areas of encephalomalacia contained large numbers of gitter cells, lymphocytes and a few polymorphonuclear leucocytes. In some parts of the encephalomalacia the gitter cells contained fine blue-staining granules of calcium. The granules of calcium were not restricted to cell bodies but were noted free in exudate surrounding the cells.

A section taken from the lumbosacral segment of the spinal cord revealed encephalomalacia of nearly the entire cord. The only uninvolved tissue was a narrow zone of white matter over the lateral and posterior funiculi (Fig. 1). The entire anterior funiculus and all of the gray matter were completely destroyed (Fig. 6). Only one nerve cell was identified in the section. In the areas of destruction there were some areas of necrosis that resembled caseation in which there was seen much fragmented chromatin material and cellular debris. Generally, however, the involved nervous tissue was packed with pathologic cells most of which were vacuolated macrophages. Plasma cells, lymphocytes and polymorphonuclear leucocytes were infrequently seen. The subarachnoid space contained scattered lymphocytes, macrophages and plasma cells. In the uninvolved part of the spinal cord there were many scattered focal glial nodules and the perivascular spaces around the blood vessels were filled with large numbers of lymphocytes and plasma cells.

Extra- and intracellular organisms identifiable as *Toxoplasma* were found in the lesions of the cord and in the brain.

*Pathologic diagnoses.* These were toxoplasmic encephalomyelitis, internal hydrocephalus, interstitial myocarditis, interstitial nephritis, focal atelectasis of the lungs and focal hemorrhages in the mucosa of the urinary bladder.

#### *Summary of case*

A seven weeks old white male infant had failed to gain weight since birth and developed a severe upper respiratory infection. A slight internal hydrocephalus was present on admission and the head gradually increased in size. Symptoms of a spinal cord lesion developed with paralysis of the upper extremities. Incontinence of both bladder and rectum appeared, the respirations became shallow and the patient expired. At autopsy there was marked internal hydrocephalus and numerous areas of encephalomalacia in the cerebral and temporal lobes which were surrounded by sharp yellow areas. Many of these areas showed fine calcium deposits and were surrounded by glial nodules. This same type

of destruction was present in the spinal cord. Microorganisms identified as *Toxoplasma* were demonstrated in the lesions of the brain and the spinal cord.

### *Comment*

This case is similar to Case III in that the disease did not become apparent for five weeks after birth. However, the failure to gain weight and the presence of the internal hydrocephalus on admission to the hospital are evidence that the infection had been progressive and present for some period of time. The pathologic changes in the spinal cord consisting of extensive myelomalacia with cellular infiltration were most advanced (Fig 1). Unusually large numbers of parasites were present in these lesions, occurring as pseudocysts and as free organisms.

*Case V* (St. Louis County Hospital No 43988) A white female infant was delivered spontaneously on June 7, 1941 and died three hours later on the same day.

*Family history* The parents had lived in St. Louis for the past five years. Previous residences were not given. The father was employed at a steel foundry and the mother had no employment outside of her household duties. Both were in good health. There had been no history of chronic illnesses in the family.

*Prenatal history* There was one child two years of age who was living and in good health. However, the mother had a history of five miscarriages dating back to 1937 when she lost her first pregnancy after 2½ months' gestation. The second miscarriage was in 1938 after two months' gestation. During the year 1940 the mother entered the St. Louis County Hospital with vaginal bleeding in the second month of her third pregnancy. A diagnosis of incomplete abortion was made and dilatation and curettage were performed. During the same year she had two other miscarriages, one at three months and the other at four months. No cause for these miscarriages could be determined and induced abortion was strongly denied. The pregnancy resulting in the patient reported here had been uneventful except for some swelling of the ankles and backache in the last trimester. The mother had gained 18 pounds during her pregnancy. She entered the hospital two weeks before the estimated date of confinement after the membranes had ruptured spontaneously. Active labor had begun before admission. Physical examination was essentially negative. She was given 1½ grains of Delvinal one hour before and open drop ether was used at the time of delivery.

*Delivery* The infant was delivered from a left occiput anterior position, Ritgen's maneuver being employed. The infant was extremely cyanotic and did not respond to ordinary stimuli. Contrast baths, coramine, metrazol and intratracheal CO<sub>2</sub> + O<sub>2</sub> were administered and respirations were improved but they remained remarkably shallow. The infant was placed in an incubator and the cyanosis gradually disappeared. CO<sub>2</sub> + O<sub>2</sub> were given every fifteen minutes but short periods of apnea began to develop which gradually became longer and the patient died during one of these periods, three hours after birth.

*Autopsy* Washington University Autopsy #9230 Postmortem examination was performed seven hours after death. The body was that of a well developed, white female infant, weighing 3100 grams. The eyelids were swollen and tightly closed by a dry, yellow, granular exudate. When the lids were forcibly separated, a moderate amount of mucopurulent exudate was seen in the conjunctival sac and the vessels of the sclera were markedly dilated. The liver and spleen weighed 150 grams and 12 grams, respectively, and there was nothing unusual noted on section. After removal of the calvarium a small amount of clotted blood was seen on the falx cerebri and on the tentorium cerebelli.

The brain was removed without difficulty. The weight of the brain was normal, being 320 grams. A few small areas of subarachnoid hemorrhage were seen over the cerebral hemispheres. Sections through the brain revealed the lateral ventricles moderately dilated with a moderate thinning of the white matter of the cerebral cortex in the region of the centrum ovale. The thinning was most marked in the temporal and parietal lobes. A small amount of gray-white exudate was noted on the ependymal surfaces of the lateral ventricles and in the right lateral ventricle there were just visible ulcers on the surface. The largest measured 6 mm in diameter.

*Microscopic examination* A section of lung disclosed the alveoli partially collapsed and containing strands of fibrin, a small amount of fine protein precipitate of edema fluid with scattered polymorphonuclear leucocytes. Sections taken from the other viscera were not remarkable. Sections taken from ulcerations in the wall of the lateral ventricle revealed a peripheral zone of caseation with a larger zone of granulomatous tissue beneath (Figs 2 and 5). The granulomatous tissue was composed of large macrophages, lymphocytes, plasma cells and fibroblasts. Scattered in the area of caseation and in the granulomatous reaction were many small granules of blue-staining calcium. The granules of calcium were in many instances found within the macrophages. Many organisms identifiable as *Toxoplasma* were found in intra- and extracellular positions in the granulomatous tissue. Several cysts containing 10 to 30 organisms but without well defined capsules were noted among the cells (Fig 8). Glial nodules were found in the brain tissue surrounding the ulcers. A section taken through the cerebral cortex revealed focal areas of destruction of the nerve cells in the cortex with replacement by large numbers of vacuolated macrophages, astrocytes and lymphocytes. There were present numerous small granulomatous lesions scattered in the white matter. The leptomeninges contained a few lymphocytes, plasma cells and vacuolated macrophages.

*Pathologic diagnoses* These were toxoplasmic encephalomeningitis, internal hydrocephalus, slight, ulceration of the ependyma of the right lateral ventricle, chronic ependymitis, clotted blood beneath the tentorium cerebelli and around the falx cerebri, and bronchopneumonia.

#### *Summary of case*

A white female infant was delivered spontaneously and was cyanotic at birth. Respirations responded weakly to strenuous attempts at resuscitation.

but periods of apnea developed which gradually became prolonged and the infant died, three hours after birth. Autopsy revealed a small amount of clotted blood on the falx cerebri and the tentorium cerebelli, with a few scattered areas of subarachnoid hemorrhage. There was slight internal hydrocephalus with focal ulcerations of the ependyma and a grayish white exudate on the surface. Microorganisms identified as *Toxoplasma* were observed in the lesions. Although there was an accompanying bronchopneumonia no organisms were found in the lungs.

### *Comment*

Fifteen months after the birth of this infant the mother re-entered the St Louis County Hospital in active labor and at full term. Her pregnancy had been uneventful except for severe headaches and dizziness one week before admission. The baby was delivered spontaneously and the mother and infant were discharged from the hospital two weeks later. The infant was considered normal in all respects. Since the diagnosis of toxoplasmosis was so clearly established in the preceding infant, attempts have been made to contact the mother for the purpose of studying her and the infant for the presence of a latent infection, but at the time of writing these have been unsuccessful.

### III THE INCIDENCE OF TOXOPLASMIC INFECTIONS

Extensive surveys which would afford information regarding the exact incidence of toxoplasmic infections have not been performed in large groups of population but the studies of Sabin (75) and Callahan (8) have shown that this type of infection is more widespread than is generally realized. Sabin (74) performed neutralization tests on 151 individuals which were selected from the following groups: 1) infants or children having one or more of the manifestations that are now considered to constitute the clinical tetrad of congenital toxoplasmosis, i.e., hydrocephalus or microcephaly, cerebral calcification, chorioretinitis, convulsive seizures, etc.; 2) the mothers of such infants or children; 3) mothers who had given birth to anencephalic monsters; 4) older children and adults exhibiting chorioretinitis of unknown causation but resembling the type encountered in infants with congenital toxoplasmosis; 5) children hospitalized during the summer and autumn of 1939 because of an encephalitis having a clinical resemblance to the proved fatal case of toxoplasmic encephalitis which he observed at that time; 6) certain unexplained cases of encephalitis; 7) children and adults who had febrile illnesses of unknown causation, obscure disturbances of the nervous system, congenital cataracts or other disturbances of the eyes, etc.

The sera of 59 of the 151 individuals studied had neutralizing substances for *Toxoplasma* and positive reactors were found in all the groups listed above. In the group of infants and children tested the incidence of neutralizing antibodies was found to be high only when certain clinical signs were present. With one exception the infants who exhibited either chorioretinitis in the macular region or cerebral calcification or both in association with other signs and symptoms possessed neutralizing antibodies in their serum. The sera of 8 of the 10 mothers



of these infants tested also revealed neutralizing antibodies. In one other case the serum of the father and older, apparently normal, siblings contained Toxoplasma neutralizing antibodies. This finding suggests that a mild subclinical infection may exist without producing characteristic signs or symptoms of the disease. Nine of ten individuals with chorioretinitis of unknown causation but morphologically resembling the type seen in congenital toxoplasmosis showed neutralizing antibodies in their serum. In 4 instances in which the ocular disturbance was thought to be congenital the mother also possessed toxoplasmic neutralizing antibodies. Three of 4 mothers who had given birth to hydrocephalic or microcephalic infants that were stillborn or died soon after birth gave positive tests as did 3 of 8 mothers who had given birth to anencephalic monsters. Various other groups of individuals including children with acute encephalitis, older individuals with unexplained encephalopathies, a boy who had recovered from atypical pneumonia and laboratory workers exposed to rabbits or to Toxoplasma gave positive neutralization tests. The study was not regarded as sufficiently extensive for a definite conclusion regarding the incidence of Toxoplasma neutralizing antibodies in the population at large. However, it is a startling revelation that there was approximately 10 per cent of individuals having neutralizing antibodies when those cases having clinically manifest toxoplasmosis were excluded.

Because of the large number of cases observed in St. Louis a survey was undertaken to determine the incidence of persons living in this vicinity (8) who had Toxoplasma neutralizing antibodies in their serum. Sera were obtained from 26 unmarried girls between the ages of 17 and 24 years who lived outside of the state of Missouri, from an equal number of unmarried girls in the same age groups who had been residents of St. Louis since birth, and from 25 married women in the same age group who had one or more normal children. The sera of 23 men between the ages of 20 and 28 years were also tested. Two unmarried girls of 18 and 21 years gave positive neutralization tests. These two individuals had been residents of St. Louis all their lives and no history of present or past illness could be obtained that might possibly be interpreted as a toxoplasmic infection. Careful physical examinations including ophthalmologic studies were negative. Even though the results of this study, indicating that 2.7 per cent of the individuals had neutralizing antibodies in their serum, are small and cannot be applied to the general population in St. Louis, it can be conservatively concluded that a significant number of individuals living in the St. Louis area have neutralizing antibodies in their serum.

Sabin (72) has shown in monkeys that the Toxoplasma neutralizing antibody persists long after the organism has disappeared from the tissues, so that the presence of antibody alone is not indicative of the presence of an infection. Moreover, it does signify that the individuals have been exposed to the specific antigenic substance of the organism at some time in the past. More exhaustive and conclusive studies on the pathogenesis of the subclinical infections and the actual incidence of the disease will be necessary before conclusions can be made. However, these results do indicate that toxoplasmic infections are more frequent than heretofore realized.

## IV EPIDEMIOLOGY

A. *Geographic distribution* Instances of infantile toxoplasmic encephalomyelitis have been observed on three continents including Europe and North and South America. Among the authenticated cases which have occurred outside of the United States, one infant was born in Prague, Czechoslovakia (28), another in Amsterdam, Netherlands (19), and a third in Rio de Janeiro, Brazil (87). The reported cases observed in the United States were in widely separated districts. Five cases have been studied in New York City (16, 98, 100, 101), one in Boston (27), another in Chicago (67), three in Detroit, Michigan (83, 107) and five in St. Louis, Missouri. Wolf and Cowen cite three unreported cases which have come to their attention, one occurring in Boston, another in Nashville, Tennessee, and the third in Dallas, Texas (16). Through personal communications with another colleague, we have learned of a case recently recognized in St. Louis, Missouri (61).

Sabin (71) has reported a fatal instance of toxoplasmic infection in a 6-year-old boy from Cincinnati, Ohio. This is the only instance of fatal toxoplasmosis in childhood.

The first proved instance of adult toxoplasmosis was reported in 1940 by Pinkerton and Weinman (62). The clinical manifestations were obscured by a concomitant infection with *Bartonella bacilliformis*. The patient was a 22-year-old laborer who died in Lima, Peru. A year later Pinkerton and Henderson (63) reported two fatal cases of toxoplasmosis occurring in adults in St. Louis, Missouri. Gumarães (22) observed the fourth instance in a negro laborer in Brazil. Recently a case of toxoplasmosis in an American soldier was observed by one of us (66). He had been stationed in New Jersey but was sent to North Africa where he became ill. The disease ran a chronic course and the patient was returned to this country, where he died. It is difficult to evaluate at which location the infection was acquired.

B. *The infection in animals* Spontaneous infection with *Toxoplasma* was first described in the gundi (North Africa) in 1908 by Nicolle and Manceaux (49) and independently in the same year by Splendore (81) in the rabbit (Brazil). Since then numerous reports of the occurrence of spontaneous toxoplasmosis in animals, reptiles and birds on many continents have been published (Table 1). The extremely wide geographic distribution and host susceptibility to these protozoan parasites affords a constant endemic focus of infection in many parts of the world.

The pathologic reports of toxoplasmic infections in animals and birds are reasonably documentary although in most instances transmission of the organism to other animals and biologic studies are lacking. Early observers who were able to recover the organism designated each newly isolated strain by the species in which the original infection occurred. Subsequent investigators (101, 70) have shown that the numerous strains such as *Toxoplasma cuniculi*, *T. columbae*, *T. gondi* and *T. musculi* were actually variously named forms of a single species capable of infecting many hosts. Comparison of the organisms recovered from

TABLE 1  
*Geographic distribution of the natural hosts of Toxoplasma*

COUNTRY	ANIMAL	BIRD	REPTILE
United States	Dog (55) Cat (55) Rat (57) Sheep (55) Guinea pig (69, 40)	Canary (23, 26, 38, 104) Sparrow (54) Catbird, chipping sparrow, king bird, red-eyed towhee, song sparrow, swamp sparrow, Baltimore oriole, cowbird, Savannah sparrow (28) House finch (105)	
Argentina		Canary (68)	
Brasil	Dog (9) Rabbit (82) Guinea pig (11)	Domestic pigeon (9) White throated seed eater, Andean white throat, white bellied swallow, Dominican cardinal, red vamp tanager, yellow finch, palm tanager (2) Rufous bellied thrush, blue black grossquit, tyrant flycatcher, white-crested elaenia, king vulture (10) Tanager (60)	
England	Squirrel (13) The Fossa (London Zoological Garden) (64) Wombat (Welcome Bureau, London) (15)	Fruit pigeon, pied bush chat (London Zoological Garden) (64)	Snake (London Zoological Garden) (64)
France	Dog (5, 48) Rabbit (34) Mouse (47) Baboon (35) Chimpanzee (29) Guinea pig (46)	Javasparrow (31)* Wax bills, weaver bird, fire finch, chaffinch (41) Yellow babbler (32)	Lizard (14)
Germany	Dog (106)	Skakin (91) English sparrow, green finch, linnet (53) Domestic fowl (24)	
Italy	Dog (43) Rat (78) Mouse (47)	European tree sparrow, Italian house sparrow (21)	
Tunisia	Gondl (49, 50, 51, 52)		

TABLE 1—Continued

COUNTRY	ANIMAL	BIRD	REPTILE
Congo	Rabbit (77)		
Senegal	Rabbit (6)		
Iran (Persia)	Dog (30)		
Gambia		African vulture (86)	
India		Domestic pigeon (42) Sparrow (1)	
Dutch East Indies	Rabbit (7)		
Japan	Mole (65)	Paddybirds, bamboo finch, Java sparrow (89)	
Formosa		White eye (88)	

\* In the original report the parasites were not identified as *Toxoplasma* but Wenyon (96) has subsequently regarded them as such

fatal human cases with those causing spontaneous infections in animals has shown no significant differences in their morphologic characteristics and biologic properties. This evidence indicates that the strains of *Toxoplasma* isolated from both animal and human infections represent a single species which has an extremely low host specificity.

A wide variety of pathologic changes have been observed in naturally infected animals. The clinical manifestations shown by infected animals are dependent upon the various organs involved and the type of change produced in the tissues. An acute type of encephalitis has been observed in rats by Perrin (57) but other tissues were not examined in detail. Acute encephalomyelitis is known to occur in sheep, rabbits, mice and guinea pigs. In contrast to this type of reaction toxoplasmic infections in dogs and cats produce granulomatous lesions in the intestines, lymph nodes, liver and lungs. The central nervous system shows minimal involvement with only an occasional "cystlike" aggregation of the organism present and only slight reaction produced in the surrounding tissues. The most commonly encountered pathologic changes are focal granulomatous lesions which may or may not show necrosis. The infiltrating cells are lymphocytes, plasma cells and large mononuclear cells. In early lesions, which have not become necrotic, a few polymorphonuclear leucocytes, particularly eosinophils, are present. The lungs, liver, lymph nodes, spleen and intestines show the most conspicuous changes. Widespread necrosis of the lymph nodes with parasitism of the reticulo-endothelial cells is commonly observed. There is an acute enterocolitis with focal ulceration of the mucosa. Lesions in the liver and spleen consist of focal granulomas with necrosis. In contrast to the infection as it is observed in man there is more extensive involvement of the parenchymatous organs and less tendency to produce damage to the central

nervous system Although parasites may frequently be observed in organs other than the brain in man there is usually little cellular reaction other than an interstitial type of inflammation. In addition to the lesions described above the parasites are frequently found in the circulating blood of reptiles and birds. However, the greatest care must be exercised in identifying the organisms as other parasites have been confused with *Toxoplasma* (103). Experimental toxoplasmic infections in rabbits, mice and guinea pigs produce the same type of cellular response but the most extensively involved parts of the body depend upon the site of the inoculation.

The manner of transmission of the infection from animal to animal is unknown. Attempts have been made to transmit the disease using commonly encountered ectoparasites such as fleas, lice and mites but these have been unsuccessful. Olafson and Monlux (55) have emphasized the importance of infected excretions as a method of transmission of toxoplasmic infection from one animal to another. These observers placed an experimentally infected puppy in a cage with six litter mates which had not been inoculated. The infected animal developed a severe diarrhea and four weeks later the other animals became ill and died within seven weeks. Postmortem examinations established the diagnosis of toxoplasmosis in the six litter mates. The cages were known to be infested with fleas and flies but none of the animals in adjacent cages developed the disease. It can be inferred from these observations that *Toxoplasma* is present in the intestinal contents of infected dogs and that the infection is acquired by ingesting food contaminated with infected excreta, although better controlled experiments are needed to confirm this idea.

**C Epidemic status** Our knowledge of the epidemiology of toxoplasmosis is extremely meager because of lack of adequate work bearing on this aspect of the disease. The occurrence of toxoplasmic infection in lower animals suggests that they may serve as a reservoir of the disease and that it may be transmitted to man by some intermediate arthropod vector or by direct contact. Various ectoparasites have been studied regarding their possible rôle as vectors of toxoplasmosis. Chatton and Blanc (12) collected a number of insects which were common parasites of the gundi, in which spontaneous infection with *Toxoplasma* is known to occur. These included two species of ticks, two species of mosquitoes, a mite and a flea. One species of tick (*Rhipicephalus sanguineus*) was particularly prevalent and was a common parasite to other animals frequently infected with *Toxoplasma*. All attempts to recover *Toxoplasma* from the ticks by direct examination and by animal inoculation were unsuccessful. However, the more recently reported cases of human toxoplasmosis (63) occurring in 2 adults with an antecedent history of the removal of engorged ticks a few days before the onset of illness lends strength to the possibility that the disease may be tick borne. The possible rôle which mosquitoes may assume in the transmission of the disease has not been adequately investigated. Chatton and Blanc (12) discuss the possibility of a mite as a vector of toxoplasmosis but there is no experimental evidence to support this assumption. Judgment regarding insects as vectors of the disease must be reserved pending further investigation.

The most convincing evidence regarding the transmission of the disease is the

observation of Olafson and Monlux (55) The demonstration of ulcerative lesions in the intestines of dogs and cats spontaneously infected with *Toxoplasma* suggests that transmission would be possible through infected excreta There has been no experimental work to substantiate this theory The demonstration of *Toxoplasma*-laden macrophages in the alveoli and bronchioles by Pinkerton and Henderson (63) suggests droplet infection as another possible method

No significance can be attached to the seasonal incidence of the disease, as it apparently occurs at all times of the year However it is most commonly observed in the periods between April and August and between December and February

The widespread geographic distribution of toxoplasmosis in animals corresponds in general to the reported instances of human infection Although the rôle of insects as vectors of the disease has not been established there is presumptive evidence to indicate that they may play a part in its transmission The pathologic changes and clinical symptomatology that have been observed in animal and human infections with *Toxoplasma* are compatible with transmission by either droplet infection or contact with infected excreta Further investigations are necessary to establish either of these methods of transmission for the naturally occurring infections in man and animals

*D Age* The onset of the clinical signs and symptoms in the infantile type of toxoplasmic infection usually occurs at the time of birth or shortly thereafter In one instance (39) hydrocephalus was present in utero, necessitating cranioclasia before the infant could be delivered The longest latent period before the appearance of symptoms after birth, which has been reported, is six weeks This was observed in 2 cases Of the 18 reported cases 13 showed signs immediately following delivery, 1 within 9 days and 1 in 35 days The age at the onset of the clinical signs and symptoms apparently has no relation to the severity of the disease The extensive destruction of the central nervous system, which is present in infants at the time of birth, is irrefutable evidence that the infection was present and progressive before birth The time of development of the clinical manifestations of the disease is largely dependent upon the parts of the central nervous system which are involved

The age of onset of the childhood type of toxoplasmic infection is difficult to ascertain Moreover it is even more difficult to ascertain if the infection is a reactivated latent congenital one or was acquired after birth Since only one fatal instance of this type of toxoplasmosis has been observed there is little material for analysis Sabin (71) was unable to reach a satisfactory conclusion as to the congenital or acquired nature of the infection in this case However, he did call attention to the differences in the types of pathologic change in the central nervous system of infants with the congenital type of infection and in the case he observed The difference in the pathologic changes in this case and in the congenital infections can be interpreted as evidence that the infection was not of congenital origin

Since the adult type of toxoplasmosis is believed by Pinkerton and Henderson (63) to be an acquired infection, this type of the disease may occur at any age

E *Sex and race* Eleven of the 18 reported instances of congenital toxoplasmic encephalomyelitis occurred in female infants. The intrauterine inception of the disease leaves the sex incidence to chance if the infection occurs through the placenta or fetal membranes. In the acquired form of the disease the method or route of infection is unknown, but of five reported cases one occurred in a woman. It can be concluded from the available information that there is no reason to believe that either the congenital or the acquired forms of transmission have a sex incidence. The majority of toxoplasmic infections have been observed in the white race although instances of both the congenital (56, 107) and acquired (22) types have occurred in the negro. Because the number of cases is small it is impossible to draw any conclusions about racial susceptibility to toxoplasmic infection.

#### V ETIOLOGIC AGENT

A. *Morphology of the parasite* In fresh preparations and air-dried films toxoplasmas appear as distinct, sharply outlined, crescentic organisms measuring 4-7 microns in length and 2-4 microns in width. The cytoplasm is distinct and clear and there is a well defined nuclear chromatin. Multiplication is by longitudinal binary fission. There is no positive evidence of schizogony. Forms of the parasite which have recently undergone division are crescentic or curved masses of cytoplasm with one extremity sharply pointed and the other rounded. Each parasite contains a rounded mass of chromatin which is situated near the center or slightly toward the rounded end. This chromatin body may appear granular and preparatory to cell division assumes an elongated shape with bullous ends. No locomotive organs are present and there is no evidence of self propelling motion. Before division the organism loses its crescentic shape and becomes oval or rounded. In Wright and Giemsa-stained smears the cytoplasm is a pale blue while the chromatin material is dark red to purple. In tissue sections which have been fixed in 10% formaldehyde, Zenker's fluid or Helly's fluid, the organisms appear smaller because of shrinkage of the cytoplasm and the nucleus. The morphology of the organism is also slightly altered by fixation (Figs 10, 12, 14). Although the shape of the parasite is preserved there is apparently greater shrinkage of the nuclear chromatin than of the cytoplasm as a clear halo is present around the nucleus. The cytoplasm is frequently studded with small, poorly staining granules. In addition to single parasites, large aggregations or clusters of closely approximated organisms are frequently observed (Fig 11). Occasionally such aggregations of parasites appear to be surrounded by a cyst wall and hence are frequently referred to as cysts or pseudocysts (Fig 13). Whether they possess a true cyst wall is uncertain, although it probably represents the cytoplasmic membrane of a pre-existing cell which has been parasitized and in which the organisms have multiplied. It is not always possible to distinguish clearly between the individual parasites within the pseudocysts as they appear to be differentiating from an amorphous mass of nucleated cytoplasm. This has led Wolf, Cowen and Paige (100) and others to suggest reproduction by schizogony. Toxoplasmas have affinities for practically all types of fixed tissue cells, particularly those of the reticuloendothelial system and the par-

enchymal cells of many organs. When there is overwhelming infection or the organism is particularly virulent, fixed tissue cells are invaded. The parasites multiply rapidly by binary fission with resulting rupture of the cell membrane and again freeing of the individual organisms to invade other cells. On the other hand, particularly in the congenital type of toxoplasmic infections, reproduction within tissue cells other than the central nervous system frequently proceeds slowly and the finding of an aggregation of parasites within the cells of the liver or heart may be accompanied by no cellular reaction in the surrounding tissue (Fig 9). In this manner chronic infections with *Toxoplasma* may be present for long periods of time in animals without producing outward manifestations of disease.

*B Propagation of the parasite* Numerous attempts have been made to cultivate *Toxoplasma* on artificial media but none have been successful. The organism has been grown on the developing chick embryo and in a medium consisting of surviving tissue (minced chick embryo suspended in Tyrode's solution). Because of the inability of *Toxoplasma* to grow on ordinary culture media it must be maintained by passage through susceptible laboratory animals. The pathogenicity of *Toxoplasma* for a large variety of commonly used laboratory animals allows the organism to be maintained with relative ease. However, care should be taken to exclude the possibility of spontaneous infection of the animals used. Infected tissue may be suspended in veal infusion broth, Tyrode's solution or in other nutritive media and stored in a refrigerator at from 2° to 10°C for as long as two weeks before further passage to other animals. However, the organisms are more delicate than viruses or other intracellular microorganisms and cannot be preserved in the frozen state. Detailed descriptions of the methods of preservation and propagation of *Toxoplasma* have been given by Sabin (76) and Wolf, Cowen and Paige (101).

*C Differential diagnosis* Since both *Toxoplasma* and *Encephalitozoon* are found as spontaneous infections in laboratory animals care must be taken to differentiate clearly these two organisms. Perrin (59) has made a careful comparative study and points out the sharp distinctions between them. The following is a list of the more important distinguishing characteristics of each parasite.

<i>Toxoplasma</i>	<i>Encephalitozoon</i>
1 Size 2-3 microns in width 4-7 microns in length	1 Size 0.8-1.2 microns in width 2-2.5 microns in length
2 Crescentic or curved	2 Straight or slightly curved
3 Occur in "pseudocysts" Individual forms poorly defined	3 Occur in "pseudocysts" Individual forms clearly defined
4 Stains deeply with hematoxylin-eosin	4 Stains faintly with hematoxylin-eosin
5 Destroyed by freezing	5 Not destroyed by freezing
6 Calcification may be present in central nervous system	6 Calcification not present in central nervous system
7 In general produces a severe necrotizing type of reaction	7 Cellular reaction is usually less severe but occasional necrotic focus may be present



## VI PATHOLOGIC ANATOMY

*A Pathologic changes in the central nervous system in infantile toxoplasmosis*

1 *Leptomeninges* The severity of the cellular reaction in the leptomeninges is dependent upon the amount of damage to the underlying brain tissue. Over unaffected parts of the cerebral cortex there is swelling of the cells of the leptomeninges and occasional foci of plasma cells, lymphocytes and mononuclear cells. In contrast, the pia arachnoid overlying destructive cortical lesions shows remarkable change, there being congestion of the vessels with infiltration of large numbers of lymphocytes, plasma cells, mononuclear cells, fat-laden macrophages and eosinophilic leucocytes (Fig 3). This type of change is particularly prominent around the small arterioles, venules and capillaries. Where the reaction is most severe there is complete obliteration of the gyri and sulci and the usually well defined line of demarcation between the pia arachnoid and the brain substance is obscured. The blood vessels of the leptomeninges show hyperplasia of the intimal cells and congestion, but rarely to the point of occlusion. Parasites are frequently found within the intimal cells of the arterioles, venules and capillaries.

2 *Cerebral cortex* The pathologic changes within the gray matter of the cerebral cortex vary from small foci of cellular infiltration (Fig 7) to large zones of necrosis with extensive destruction of brain substance. Within the larger of these foci there is complete loss of architecture and neurons with profound alteration of the glial elements. Large clusters of nuclear debris and numerous fat-laden macrophages and eosinophils are present. In many of the necrotic foci cysts form that become infiltrated with plasma cells and lymphocytes (Fig 3). The cysts frequently contain large macrophages, lymphocytes and mononuclear cells in a network of fibrin. The brain substance immediately adjacent to the foci of necrosis is edematous and infiltrated with small numbers of lymphocytes. There is loss of neural and neuroglial elements and moderate proliferation of astrocytes. Most of the astrocytes are large and swollen and occasionally contain more than one nucleus, giving the appearance of atypical giant cells. The oligodendroglia are swollen with concentration of the nuclear chromatin. The blood vessels show hyperplasia of the intima and some infiltration with pathologic cells within the adventitia. In the more severely damaged zones there is proliferation of capillaries forming a network on which infiltrating cells are dispersed. Immediately adjacent to the large foci of necrosis there is infiltration with polymorphonuclear leucocytes, macrophages, lymphocytes and plasma cells. There is loss of many nerve cells and those remaining show vacuolization of the cytoplasm and advanced chromatolysis.

One of the consistent findings in the infantile type of toxoplasmosis is the presence of large foci of calcification within the zones of necrosis. This process may be quite extensive, forming broad bands of calcific material involving most of the cortical layers or scattered diffusely throughout the foci of necrosis. The calcium salts are deposited in coarse granules or in finely divided particles giving

the appearance of "calcium dust" Calcium may be deposited within the nerve cells of the cortical substance and occasionally is seen in microglial cells Many cells become completely calcified leaving only a small clear zone between the cell membrane and the calcific deposits, while other cells contain only a few particles of finely divided calcium The extent of the calcification is apparently dependent upon the severity of the reaction and the duration of the infection

3. *Basal ganglia* Small granulomatous lesions are scattered throughout the globus pallidus, caudate nucleus, putamen and internal capsule For the most part these granulomatous lesions consist of focal collections of lymphocytes, plasma cells and large mononuclear cells The walls of the small blood vessels and the perivascular spaces of the basal ganglia are heavily infiltrated with mononuclear cells In addition to small granulomatous lesions large foci of necrosis are usually present and are filled with eosinophilic leucocytes, degenerating lymphocytes and plasma cells Whenever large zones of necrosis are present there are numerous fat-laden macrophages In older lesions there is proliferation of new capillaries and multiplication of microglial cells At the margin of the foci of degeneration there is the same type of cellular response as is observed in the cerebral cortex There is little degeneration of myelin outside of the severely damaged areas The nerve cells are usually well preserved and contain a normal amount of Nissl substance In our experience it is relatively rare to find *Toxoplasma* within nerve cells although Gumarães (16) reports this occurrence as common Parasites are more frequently found adjacent to the areas of necrosis and near or in the granulomatous lesions

4. *Ventricles* Periventricular infiltration with lymphocytes and plasma cells with ulceration of the ependymal lining is frequently observed in infantile toxoplasmosis Ulceration is most common in the lateral and third ventricles (Figs 2 and 5) and is frequently found in the cerebral aqueduct where glial nodules and ulcerative lesions may occlude the lumen and obstruct the flow of cerebrospinal fluid (Fig 4) This readily accounts for the internal hydrocephalus observed in infants in this disease

5. *Cerebellum* There is a multiplication of leptomeningeal cells and slight to moderate degree of infiltration with plasma cells, lymphocytes and mononuclear cells in the subarachnoid space Small granulomas may be found within the substance of the cerebellum but generally the lesions in the cerebellum are infrequent and inconspicuous When present they are most frequent in the subependymal tissue adjacent to the fourth ventricle

6. *Pons* The pons is usually the site of advanced pathologic change Numerous small granulomas with large foci of necrosis are present in the tegmentum and pontine nuclei The tissue surrounding the necrotic zones is edematous and shows mild astrogliosis The cellular response to the parasite is the same as that observed in other parts of the central nervous system In the cases which we have studied the severity of the disease in the pons has been second only to pathologic changes in the cerebrum Cyst formation in the tissue is frequent in the pons and medulla

7. *Medulla* The medulla has been involved in all cases of infantile toxoplasmic

infection in which it has been studied. The degree of involvement varies somewhat but in general the inflammatory reaction in this part of the central nervous system is severe. The lesions are identical in all respects with those observed in the other parts of the brain.

8 *Spinal cord* The leptomeninges show a varying degree of pathologic change depending upon the amount of destruction in the underlying spinal cord. The spinal roots are not involved except secondarily in parts where there is great destruction of nervous tissue. The degree of change in the spinal cord is extremely variable. It may consist of focal infiltration with lymphocytes and plasma cells or of extensive areas of myelomalacia involving the entire diameter of the cord (Figs 1 and 6). The cellular response in the spinal cord is the same type as that observed in the brain with the exception that polymorphonuclear leucocytes are more frequent and constitute the majority of the infiltrating cells. Parasites are numerous in the lesions seen in the spinal cord, especially where the reaction is severe.

9 *Ocular lesions* The presence of parasites in the choroid and retina was observed by Jankú (28) in 1932, in the first reported instance of human toxoplasmic infection. He described the pathologic changes in the eyes but made no attempt to identify or classify the parasite. Wolf, Cowen and Paige in collaboration with Koch (30) have described in detail the only other reported cases in which ophthalmologic as well as histopathologic studies have been made of the ocular lesions. The pathologic changes consist of focal swelling of all layers of the retina with intense edema and varying degrees of inflammation with necrosis. The foci of necrosis were present in all layers to a varying degree but were most advanced in the inner layers where large zones of degeneration were observed. There was diffuse infiltration with mononuclear cells and a few eosinophilic leucocytes particularly near the margin of the necrotic foci. The perivascular tissues were heavily infiltrated with lymphocytes and plasma cells. In addition there was an accompanying hyperplasia of the endothelial cells of the vessel. An inflammatory exudate was present on the surface of the internal limiting membrane and was associated with an ingrowth of fibroblasts and capillaries into the adjacent vitreous. The architecture of the retina was distorted by the displacement of the cells of one layer into another. Many of the nerve cells had disappeared.

The choroid showed a moderate infiltration with plasma cells, lymphocytes and mononuclear cells as did the sheath of the optic nerve. Parasites were present in large numbers in the retina within the necrotic foci and in lesser numbers in the choroid.

B *Pathologic changes in the central nervous system in adult toxoplasmosis*  
In contrast to the widespread destruction of the brain and spinal cord observed in infantile toxoplasmosis the disease in adults and older children produces pathologic changes which are more manifest in the other viscera with minimal lesions in the central nervous system. In the case observed by Sabin (71) diligent search was necessary before small granulomatous and necrotic foci were identified in the brain. Parasites were also difficult to identify and were present only in

5 *Adrenals, pancreas and pituitary* Involvement of the adrenal glands by *Toxoplasma* is frequent, occurring in 40 per cent of the cases in which histologic studies have been made. The pathologic changes consist of granulomatous foci which frequently show necrosis. Parasites are frequently found in the uninvolved tissue adjacent to the inflammatory foci but rarely within them. The pancreas and pituitary contained organisms without associated pathologic changes in one instance (22).

6 *Liver, spleen and lymph nodes* The liver and spleen have been involved in all cases of toxoplasmic infection in adults. In infants the liver contained the parasites in one instance without concomitant pathologic change in the tissue. No pathologic change or microorganisms have been found in the spleen in any of the cases. The pathologic changes are essentially the same as those described in the adrenals, consisting of granulomatous foci with necrosis. Parasites have been observed in the reticuloendothelial cells as well as the parenchymal cells. The lymph nodes contained parasites in only one instance and without significant pathologic change in the surrounding tissue (22).

7 *Bone marrow* The bone marrow contained small granulomatous foci in which *Toxoplasmas* were demonstrated in two instances (22 and Case II of our series). In many of the reported cases no statement is made as to the presence or absence of lesions in the bone marrow although the presence of parasites in this readily accessible tissue would afford a rapid and easy method of diagnosis of this disease. In one of the cases there were widespread visceral lesions caused by *Toxoplasma* while, in the other, organisms were demonstrable only in the central nervous system and bone marrow. In the latter instance parasites were observed in the vertebral bone marrow as well as the mastoid process in association with an acute mastoiditis.

8 *Kidneys* Lesions in the kidneys in which parasites have been described are reported in 4 cases of toxoplasmic infection. Two occurred in infants (107, Case I) and two in adults (63, 22). In the remaining cases the pathologic changes consisted of focal granulomatous lesions with necrosis, similar to those seen in the liver and adrenal glands. The infiltrating cells were principally lymphocytes and plasma cells although polymorphonuclear leucocytes were present in small numbers within the foci of necrosis. There was a focal glomerulitis apparently caused by the presence of parasites within the swollen endothelial cells of the glomeruli. Cellular infiltration was prominent about the preglomerular arterioles and there was widespread necrosis of the proximal convoluted tubules. The medulla showed necrosis of the collecting tubules and cellular infiltration about the renal pelvis.

9 *Ovaries and testes* Cellular infiltration with small foci of necrosis has been observed in the ovaries in one case (56) without demonstrable parasites. In this instance, which occurred in an infant, there was widespread involvement with *Toxoplasma* and both lesions and parasites were demonstrable in most of the other organs. Zuelzer (107) reported the only case in which the testicles were involved. Many of the seminiferous tubules had undergone necrosis and the lumina were filled with nuclear debris, plasma cells, lymphocytes and mononu-

clear cells. The interstitial substance was diffusely infiltrated with mononuclear cells and contained many foci of hemorrhage. Parasites were identified in the exudate within the lumina and in the spermatogonia of the intact tubules.

10 *Skin and subcutaneous tissue* Toxoplasmas have been identified in the skin and subcutaneous tissues in only two cases in infants (87, 56) and there were no associated pathologic changes. In one case, reported in an adult (83), there were inflammatory foci in the dermis and subcutaneous tissues but no parasites could be identified. In this instance there was a skin rash during the clinical course of the disease.

#### VII PATHOGENESIS

*A Infantile toxoplasmosis* The early observations of Paige, Cowen and Wolf (102) have firmly established that in most instances infantile toxoplasmic infection is acquired in utero. The presence of the disease in a stillborn infant (Case IV) with the onset of clinical signs and symptoms at birth or within a few days gives evidence that the infection was present and progressive before birth. Moreover, the advanced nature of the pathologic changes observed in the central nervous system at autopsy lends further support to the assumption that the infection was acquired in utero. In one of the cases reported in this series (Case V) the infant showed signs of disease at birth and died three hours later. Extensive zones of calcification were present in the brain in association with widespread necrosis. In two additional cases signs and symptoms of the disease were present at birth, thus affording goodly evidence of a disease progressive until the time of death. The evidence in favor of the intrauterine inception of infantile toxoplasmosis is further substantiated by the presence of neutralizing antibodies for *Toxoplasma* in the blood of the mother. Paige, Cowen and Wolf (56) have demonstrated maternal antibodies in 3 instances in which the infants subsequently died of extensive toxoplasmic encephalomyelitis. Zuelzer (107) has also observed a similar case in which he was able to demonstrate the presence of neutralizing antibodies in the serum of the mother. In a second instance neutralization tests on the serum of the mother gave negative results. This was interpreted by him to be evidence that the infection was acquired post-partum. The pathologic changes observed in this case suggest that the disease was an acute process as they consisted of granulomas with foci of necrosis. No calcification was demonstrable in the brain. It is possible from this evidence that two forms of the disease are present in infants, a congenital infection which produces pathologic changes in the fetus before birth and an acquired form of the disease which is a post-partum infection. That the second form represents a reactivated latent infection of congenital origin must be considered but the absence of neutralizing antibodies in the serum of the mother does not support this idea, for which reason it is reasonable to conclude that the disease is acquired after birth. In all instances in which the mother's blood did not contain neutralizing antibodies the infants were not ill at the time of birth and the pathologic changes were those of an acute encephalomyelitis without calcification. Similar lesions have been observed in experimentally infected mice that died in

lar spasm was a common finding and first involved groups of muscles in the extremities or face and then spread to involve the entire part. Generalized convulsions were observed in 67 per cent of the cases. In most instances the

TABLE 2  
*Reported cases of infantile toxoplasmosis*

CASE NUMBER	AUTHOR	SEX	GEOGRAPHIC LOCATION	ONSET OF DISEASE	DURATION OF DISEASE	AGE AT DEATH
1	Jankó (28)	M	Prague	3 da	11 or 16 months	11 or 16 months
2	Torres (87)	F	Brazil	birth	2 da	2 da
3	Richter (67)	F	Illinois	6 wk	7 da	7 wk
4	de Lange (19)	F	Netherlands	9 da	4 mo	4 mo
5	Hertig (27)	F	Massachusetts	birth	25 da	25 da
6	Wolf, Cowen (97)	F	New York	2 da	28 da	30 da
7	Wolf, Cowen (97)	M	New York	3 da	28 da	31 da
8	Wolf, Cowen, Paige (99, 100)	F	New York	birth	9 wk	9 wk
9	Wolf, Cowen, Paige (99, 100)	M	New York		stillbirth	
10	Wolf, Cowen, Paige (99, 100)	F	New York	2 da	1½ da	3½ da
11	Steiner, Kaump (83)	M	Michigan	birth	3 da	3 da
12	Zuelzer (107)	M	Michigan	birth	11 da	11 da
13	Zuelzer (107)	M	Michigan	3 da	27 da	30 da
14	Callahan, Russell, Smith	F	Missouri	birth	4 da	4 da
15	Callahan, Russell Smith	F	Missouri	birth	67 da	67 da
16	Callahan, Russell Smith	M	Illinois	6 wk	17 da	65 da
17	Callahan, Russell Smith	M	Missouri	35 da	34 da	69 da
18	Callahan, Russell, Smith	F	Missouri	birth	3 hr	3 hr

Cases 9 and 13 were in negro infants

TABLE 3  
*Neurologic signs and symptoms in infantile toxoplasmosis*

	PRESENT		ABSENT	UNKNOWN
	Number	Per cent	Number	Number
Internal hydrocephalus	12	80	3	3
Muscular twitching	10	71	4	4
Convulsions	10	67	5	3
Spasticity	7	54	6	5
Opisthotonos	6	45	6	7
Retraction of head	4	36	7	7
Stiff neck	2	22	7	9
Paralysis	2	18	9	7

onset was insidious and gradually developed into true clonic convulsions. Stiff neck and retraction of the head were observed in from 20 to 30 per cent of the cases. The signs of meningeal involvement appeared only in those cases in which there was severe damage to the underlying nervous system. It is assumed

that the pathologic changes observed in the meninges are secondary and the result of extension of the toxoplasmic infection from the underlying nervous tissue. In 45 per cent of the cases the convulsions were so severe that the opisthotonic position was assumed shortly before death. Spinal or bulbar involvement was manifest by paralysis of the extremities, difficulty in swallowing or respiratory difficulty. The usual sequence of events was muscular twitching followed by spasticity and generalized convulsions. The other neurologic manifestations frequently did not become evident until shortly before death. Neurologic signs and symptoms were present in all but one case (Case V) in the present series. In this child there was respiratory difficulty at the time of birth and until death, three hours later.

c Ocular signs and symptoms. Koch and Wolf, Cowen and Paige (30) have carefully studied the pathologic changes observed ophthalmoscopically and have described the lesions at various stages of the disease. In five of the six cases which they report autopsies were performed and the eyes examined histologically. As seen through the ophthalmoscope the lesions are predominantly bilateral, focal and frequently multiple. The macular region in each eye is invariably involved but peripheral lesions may also occur. The earliest acute lesions which they observed were characterized by localized edema, indefinite demarcation from the surrounding retina and necrosis. Frequently chorioretinal atrophy is present to such a degree that the underlying sclera may be visualized. Foci of atrophy are frequent with extensive pigment deposits at the periphery of the lesions. Older lesions consist of sharply margined foci of chorioretinal atrophy and proliferation with diffuse irregular pigmentation. The vitreous was not involved in any of the cases.

Other ocular changes were frequently associated with toxoplasmic chorioretinitis. Microphthalmos with atrophy of the cornea was present in all cases which they examined. Atrophy of the optic nerve with varying degrees of refractive errors was usually observed. Papilledema may or may not be present, depending upon the lesions in the central nervous system. Toxoplasmic chorioretinitis must be differentiated ophthalmoscopically from 1) pseudoglioma, 2) intraocular tumor, 3) traumatic lesions, 4) hereditary macular defects and 5) congenital developmental defects of the choroid and retina.

2 Other signs and symptoms. These are collectively summarized in Table 4.

a Jaundice. Although jaundice is not an invariable finding in toxoplasmic infections in infants, it was present in 5 of 18 cases. The reasons for its occurrence cannot be satisfactorily explained except in one instance. In this case pathologic changes were present in the liver, consisting of severe degenerative changes with destruction of the hepatic architecture and swelling and vacuolation of the liver cells (107). The Kupffer cells contained granules of brown pigment and there were numerous foci of extramedullary erythropoiesis. Granulomatous lesions and parasites were not found and the author did not attribute the pathologic changes to toxoplasmic infection. In the other cases the lesions in the liver were insignificant. Toxoplasmas have been identified in the liver in one case but the organisms were within hepatic cells and there was no accompanying

cellular reaction (Case I) In three cases jaundice was severe and numerous nucleated red blood cells were present in the peripheral blood. These findings together with enlargement of the liver and spleen led to the clinical diagnosis of erythroblastosis fetalis. The pathologic findings in these cases are difficult to evaluate because of the presence of a severe toxoplasmic infection. However, in all cases unusually large numbers of foci of extramedullary erythropoiesis were present in the liver and spleen. Although these infants with toxoplasmosis could have had erythroblastosis it seems unlikely that three of them would have the disease. From the evidence available it is more probable that a severe toxoplasmic infection was the factor responsible for the pathologic changes observed.

TABLE 4  
*Systemic signs and symptoms in 18 cases of infantile toxoplasmosis*

	PRESENT		ABSENT	UNKNOWN
	Number	Per cent	Number	Number
Splenomegaly	7	50	7	4
Hepatomegaly	9	64	5	4
Jaundice	5	42	7	6
Purpuric spots	3	33	9	6
Feeding difficulty	9	64	5	4
Diarrhea	4	31	9	5
Vomiting	6	43	8	4
Upper respiratory infections	5	45	6	7
Pulmonary signs	11	73	4	3
Fever*	9	60	6	3
Subnormal temperature*	7	54	6	5

\* In two cases the temperature was extremely fluctuant and is recorded as both subnormal and elevated.

Sabin (75) suggested that *Toxoplasma* may produce some toxic substance and that the jaundice may be the result of the toxic substance acting on the liver cells. However, other signs and symptoms to indicate a toxic substance have not been observed, so judgment regarding this point must be reserved.

b Respiratory disturbances Five infants showed signs and symptoms of respiratory infection soon after birth. In three, *Toxoplasmas* have been identified in the lungs in association with an interstitial type of pneumonitis. In one additional case the typical pathologic changes of interstitial pneumonia were present but no organisms were identified. The known frequency of pulmonary lesions in animal toxoplasmosis and the occurrence of a severe pulmonary involvement in adults is good presumptive evidence that the lesions are caused by this organism. Intercurrent bacterial pneumonia may complicate the picture and make it extremely difficult to evaluate the inciting cause of the lesion.

c Temperature Five of the 18 cases had a subnormal temperature throughout the entire course of the illness, while seven developed an elevated temperature.



disease which persisted until death. In two of the cases the temperature varied so wide that it was both subnormal and elevated and in which a fever developed the temperature was extremely variable, wide variations within a 24-hour period. It may be concluded from these observations that there is nothing characteristic about the temperature in

intestinal symptoms. In 8 of the patients there was vomiting and in a few these were the first presenting symptoms of the disease. In 5 symptoms developed soon after birth and became increasingly severe as the infants were feeding problems.

**Vascular symptoms.** In one case edema of the extremities and was noted and there was an associated diffuse myocarditis in which trophozoites were found in the myocardial lesions at autopsy. Six had myocarditis. In some of the cases the lesions were focal while in others was diffuse disease that was associated with foci of necrosis. In 4 trophozoites were identified in the myocardium without accompanying electrolyte changes. Although few instances of cardiovascular disturbances were noted clinically the high incidence of involvement of the cardiac muscle justifies the conclusion that cardiac damage is a frequent complication of the disease.

**Trophozoitosis.** The clinical signs and symptoms observed in adults have been extremely variable and the number of cases is too small to draw definite conclusions. The first case described by Pinkerton and Henderson (62) was complicated by a concomitant infection with Bartonella bacilliformis so that the clinical findings cannot be accurately evaluated. In subsequent cases reported by Pinkerton and Henderson (63) the illness was characterized by sudden onset with chills and fever, and a variable but persistent elevation of the temperature throughout the course of the disease. A maculopapular eruption involving the entire body with the exception of the hands, the soles of the feet and the scalp. Pulmonary involvement was an outstanding feature of the disease, both clinically and pathologically. It was apparently caused by interference with the respiratory system (63). A diffuse interstitial pneumonitis with focal necrosis was observed in the lungs at necropsy. Numerous parasites were identified in the lesions. The clinical signs and symptoms referable to the central nervous system were so insignificant that there was no examination made of the spinal fluid. This is in sharp contrast to the disease as observed in infants where the lesions in the central nervous system comprise the principal clinical disease.

As observed in an American soldier (66) manifested entirely different signs and symptoms. After the onset of the disease it ran a chronic course with definite symptoms referable to the central nervous system. Necropsy revealed that the pathologic changes were almost entirely referable to the brain. The pathologic changes observed consisted of numerous microcephalomalacia with numerous parasites in and around the lesions.

Guimaraes (22) reported a case which was complicated by chronic malaria and the patient's course of recurring chills and fever with gradual weakness cannot be accurately determined to have been entirely due to *Toxoplasma*, although parasites were found widely disseminated throughout the body at the time of autopsy

In general from the foregoing observations it may be said that toxoplasmic infections in adults produce a variety of clinical signs and symptoms. There is more tendency in the adult type of infection for widespread involvement of the viscera than is seen in the infantile form of the disease. This is probably related to the portal of entry and the mode of infection.

#### IX LABORATORY EXAMINATIONS

*A Urine* In 3 cases inflammatory lesions in the kidney were present. In 2 there was an interstitial type of inflammation which consisted of a diffuse infiltration with lymphocytes, plasma cells and mononuclear cells. There was associated swelling of the cells of the tubular epithelium, in some instances with necrosis. The urinalyses done during these patients' stay in the hospital were negative. Zuelzer (107) reported a case in which the renal changes consisted of focal and acute necrotizing glomerulitis with necrosis of the adjacent renal tubular epithelium. Although there were significant pathologic changes in the kidneys in the aforementioned 2 cases of toxoplasmic infection, no significant changes were noted in the urine. It may be safely concluded from these observations that examination of the urine is of little or no value in the diagnosis of toxoplasmic infections.

*B Blood* Anemia was a common feature of toxoplasmosis in infants, being present in 50 per cent of the cases in which the blood was examined. The existence of anemia in newborn infants with severe infections is, however, a fairly frequent occurrence. In 4 cases nucleated red blood cells were present in the peripheral blood, although in the newborn a few normoblasts is not unusual. In 3 cases, however, the percentage of nucleated red blood cells was extremely high and was one of the determining factors in making the clinical diagnosis of erythroblastosis fetalis. In one case there was a persistent leucopenia throughout the entire course of the disease. On the other hand, 50 per cent of the cases showed a leucocytosis with a marked shift to the left. However, in 3 of these cases there was an associated bacterial infection that could have been the causative factor for the increase in the number of white blood cells. One infant showed no increase in the white blood cell count throughout the course of the disease. The differential count usually revealed an increase in the number of monocytes and an absolute rise in the number of lymphocytes. No abnormal cells or immature forms were observed in the peripheral blood. Hemorrhagic tendencies that were noted in 3 cases are difficult to explain. In one of these cases there was anemia with an associated leucopenia but a platelet count was not done. One can only assume that in this instance there was depression of all the cellular elements of the bone marrow with resulting thrombocytopenia. In one instance in which the infant was jaundiced and the liver and spleen were

enlarged no blood studies were performed although a tentative diagnosis of hemorrhagic disease of the newborn was made. In only one case has there been an increase in the number of eosinophils in the circulating blood. In general it may be stated that the hematologic picture is one of leucocytosis with an absolute increase in the number of monocytes and lymphocytes in the peripheral blood. There is usually an anemia which is frequently accompanied by hemorrhagic tendencies. However, this picture is extremely variable and is not of diagnostic significance.

C *Cerebrospinal fluid.* The cerebrospinal fluid was examined in each of the 18 cases of infantile toxoplasmosis and in each case there was an increased protein content. In none of the cases was there an elevation of the cerebrospinal sugar. Xanthochromia was present in all but one case. There was usually pleocytosis, chiefly of mononuclear cells. In general, however, the cell studies were unsatisfactory. The ventricular fluid showed essentially the same type of changes as fluid withdrawn from a lumbar tap. The ventricular fluid was xanthochromic, usually turbid with pleocytosis and elevation of the protein. The frequent association of lesions in the ependyma with ulceration of the ventricular surface of the brain is probably responsible for many of the changes that occur. Examination of the cerebrospinal fluid affords the most constant significant laboratory examination for the presence of infantile toxoplasmosis.

D *Roentgenograms.* No roentgenograms of the skull were made in the cases presented here. However the necropsy study revealed cerebral calcification in all cases to a degree that could have easily been visualized by roentgenograms had they been made. In other reported cases cerebral calcification has been observed by roentgenograms in the cerebral hemispheres, the basal ganglia, the thalamus, the caudate nuclei and in the region of the postcentral gyrus. The calcification that was observed in our cases at the time of autopsy was predominantly in the parietal and occipital regions of the cerebral cortex.

E *Immunologic studies.* Neutralizing antibodies against *Toxoplasma* are formed by the host and their demonstration is the most reliable method available for clinical diagnosis of the disease. The test for the demonstration of the presence of neutralizing antibodies affords a simple and rapid method for the presumptive diagnosis of toxoplasmosis. The details of the performance of this test will be found in papers by Wolf, Cowen and Paige (101), Sabin (74), and Callahan (8). The test is performed on the skin of the rabbit and various dilutions of a suspension of *Toxoplasma* are mixed with a given amount of the prepared serum. The presence of neutralizing antibodies prevents the formation of a necrotic lesion on the skin of the rabbit. A control using Tyrode's solution, broth or saline is used. This test promises to be of real value in future work concerning the incidence of toxoplasmosis in large groups of population.

#### X NONFATAL INSTANCES OF HUMAN TOXOPLASMOSIS

In 1942 Cowen, Wolf and Paige (16) reported 6 cases of toxoplasmic infections in children. This contradicted the conclusion reached from their previous studies indicating that the infection was uniformly fatal. These cases showed

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## OSTEOMALACIA AND LATE RICKETS

THE VARIOUS ETIOLOGIES MET IN THE UNITED STATES WITH EMPHASIS ON THAT RESULTING FROM A SPECIFIC FORM OF RENAL ACIDOSIS, THE THERAPEUTIC INDICATIONS FOR EACH ETIOLOGICAL SUB GROUP, AND THE RELATIONSHIP BETWEEN OSTEOMALACIA AND MILKMAN'S SYNDROME<sup>1 2 3</sup>

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Osteomalacia and its counterpart in growing children, so called "late rickets", are usually considered very rare conditions in the United States, they are rare but not very rare. The diagnosis is often missed, which is unfortunate since the treatment is eminently successful. It is the purpose of this paper to trace several pathological sequences which lead to this osseous abnormality, to emphasize one sequence in particular dependent on a particular form of renal acidosis, to outline the therapy for each of the etiological sub-groups, and to point out that Milkman's Disease is a form of Osteomalacia.

### DEFINITION AND NATURE OF OSTEOMALACIA

Osteomalacia ("adult rickets") is a disorder of bone tissue characterized by a failure of calcium salts to be deposited promptly in the newly formed bone matrix (osteoid). The reason for this failure is to be found in the body fluids which contain too little calcium for the level of inorganic phosphorus or, to place the emphasis differently, too little inorganic phosphorus for the level of calcium to allow for normal precipitation of whatever salt of calcium it is that is precipitated into bone matrix. The serum calcium level is normal or low, the serum phosphorus<sup>4</sup> level is low or normal, in any case the product of the serum calcium in mg and the serum phosphorus in mg is lower than normal. Furthermore, the failure of the bone to be calcified (or phosphorized) leads to weakened bones, this leads to an increased activity of the osteoblasts, this in turn leads to a high

<sup>1</sup> A part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the Massachusetts General Hospital. The expense of these studies was partly defrayed by grants from the Josiah Macy, Jr. Foundation, the National Research Council (Committee for Research in Endocrinology), and the Mary Gove Pittman Fund. A bed supported by the Mallinckrodt Chemical Company on the Metabolic Ward was used for part of these studies.

<sup>2</sup> Aside from various individuals whose names are mentioned in parts of the paper, the authors are indebted to Esther Bloomberg, Dorothy F. Bryant, Eleanor F. Dempsey, and Lowell D. Cox for technical assistance.

<sup>3</sup> An abstract of this paper was read before the American Academy of Pediatrics by one of us (F. A.) as an invitation paper connected with the Mead Johnson Award for 1944.

<sup>4</sup> Henceforth in this paper by "serum phosphorus" is meant serum inorganic phosphorus.

serum alkaline phosphatase level Rickets has all the characteristics of osteomalacia plus some additional changes at the growing epiphyseal cartilage, notably faulty calcification of the zone of provisional calcification

#### DIFFERENTIATION OF OSTEOMALACIA FROM OSTEOPOROSIS AND OSTEITIS FIBROSA GENERALISATA

Osteomalacia is to be differentiated from two other chronic metabolic disorders likewise characterized by too little completed bone tissue These are osteoporosis and osteitis fibrosa generalisata

In osteoporosis the decrease of bone tissue is due to the fact that the osteoblasts lay down too little bone matrix, that matrix which is laid down is normally calcified Thus, since osteoporosis is a disorder of tissue metabolism, not of calcium or phosphorus metabolism, one is not surprised to find normal serum calcium and phosphorus levels The serum alkaline phosphatase level, the index to osteoblastic activity, is likewise normal,—not low as one might at first thought expect A normal phosphatase level really means a relatively low level if one considers the fact that the skeletal mass, being decreased, is more subject to stresses and strains, the usual stimulus to osteoblasts

In osteitis fibrosa generalisata the decrease in bone tissue is due to increased bone resorption, not decreased bone formation as in osteomalacia and osteoporosis The increased bone resorption leads to decreased bone strength and this in turn leads to an increased activity on the part of the osteoblasts and hence to a high serum alkaline phosphatase level The commonest cause of osteitis fibrosa generalisata is hyperparathyroidism which, if present, is associated with a low serum phosphorus and a high serum calcium level

In summary, therefore, the expected findings in osteomalacia are a normal or low serum calcium, a low or normal serum phosphorus (most commonly a normal serum calcium with a low serum phosphorus), and a high serum alkaline phosphatase level, in contrast to these findings are the normal serum calcium, phosphorus, and phosphatase levels in osteoporosis and the high serum calcium, low serum phosphorus and high serum phosphatase levels in osteitis fibrosa generalisata when the latter is due to hyperparathyroidism

#### IS MILKMAN'S SYNDROME A FORM OF OSTEOMALACIA?

In 1930 and 1934 Milkman (1, 2), under the designations of "Pseudofractures" and later of "Multiple Spontaneous Idiopathic Symmetrical Fractures", described a chronic condition of bone, the true nature of which, if one is to judge by a recent article by Edeiken and Schneebug (3), has remained somewhat obscure

Milkman's classical case (1, 2) was that of a woman of forty-three with a past history of the passing of renal calculi, whose first symptoms were pain in the lower back and extremities and a waddling gait No skeletal abnormalities were recognized by x-ray during the first two years of her illness, thereafter "ribbon-like zones" of decalcification, many of them symmetrical, appeared The patient died after six years of generalized pains By that time forty-three bony defects were present but the skull and pelvis remained uninvolved Of interest among

the autopsy findings were "diffuse nephritis" and the diagnosis of osteomalacia by two of three pathologists. Milkman emphasized the absence of bone deformities and the late occurrence of bone displacement, and defined the syndrome as a "systemic disease involving the entire skeleton, flat and tubular bones, with symmetrical fractures starting in the cortex". Not emphasized by Milkman and possibly of importance in view of the discussion to come concerning renal acidosis and Fanconi Syndrome, were the diffuse nephritis, the history of passing stones, and the finding of intermittent but rather marked glycosuria (up to 5%) and ketonuria in the presence of normal fasting blood sugar levels.

The first question is: are the findings in Milkman's Syndrome due to osteomalacia? The authors feel certain that they are. This conclusion is based on four considerations: a) the symmetrical ribbon-like zones of decalcification, seen by x-ray and often occurring in otherwise normal appearing bone, are characteristic of osteomalacia and of that disease alone; b) the serum calcium, phosphorus, and phosphatase findings in most of the undoubted cases are those of osteomalacia; c) such patients respond to therapy based on the assumption that they have osteomalacia; and d) the histo-pathology, if carefully studied, is that of osteomalacia. These items will now be discussed one by one.

The formation of bone consists of two steps: laying down of the matrix by the osteoblasts and the calcification of the matrix. In osteomalacia the first of these steps is intact, the second deficient. The healing of a fracture consists of the same two steps. In a fracture complicating osteomalacia one would anticipate that the first step would proceed normally, or even better than normally in view of the increased number of osteoblasts, whereas the second step would be faulty. Such has been shown to be the case in experimental osteomalacia in rats. Ham, Tisdall, and Drake (4) did a very simple and conclusive experiment on rats. Fractures were produced in a group of rachitic rats, x-rays at the end of three weeks gave the impression that no union had taken place, histological studies, however, showed the presence of excellent calluses which were not calcified, similarly treated animals, allowed to live four days longer and given vitamin D, showed rapid calcification of the calluses but little change in their histological appearance. Thus, if a fracture without displacement were to occur in a patient with osteomalacia, one would expect union to occur but the zone of callus formation to remain uncalcified.

But do such fractures occur in undoubted cases of osteomalacia in humans? The answer is yes. The subject has been extensively discussed in the German literature, notably by Looser (5, 6) who characterized such united but uncalcified fractures as "Umbauzonen" (zones of transformation). To be sure, it was not Looser's conception that the first step was an actual fracture, he conceived of the process as a "slowly progressing callus formation inside the bone" brought about by a "mechanical irritation due to strain" and by "small local inflections". The net result is a local "transformation of bone". By transformation (Umbau) of bone he meant a change from lamellar bone to that characteristic of a callus, namely braided (geflechtartig) bone. This author goes on to state that "since the callus

in osteomalacia remains uncalcified for a long time, it is understandable why the zone of bony transformation remains for a long time after its formation as a zone of decreased density by x-ray "

From the above discussion it seems clear that the ribbon-like zones of decalcification characteristic of Milkman's Syndrome are consistent with an underlying osteomalacia. The question arises as to whether they are found in any other systemic bone disease. It is the authors' opinion that they are not. In this respect, the authors are in disagreement with the conclusions of Camp and McCullough (7) who, in a most informative and valuable paper, speak of the lesions under discussion as "pseudofractures" and emphasize the fact that they occur in a great variety of conditions, these, they state, include osteomalacia, rickets, late rickets, celiac disease, chronic idiopathic steatorrhea, Gee's disease, non-tropical sprue, severe chronic acidosis or hyperglycemia, renal rickets, early and late osteogenesis imperfecta, fragilitas ossium, hyperparathyroidism, hyperthyroidism, osteitis deformans (Paget's disease), adrenal-pituitary bone dystrophy, congenital syphilis, osteomyelitis, osteopetrosis (marble bone), march fracture, and certain blood dyscrasias. It should be pointed out that the bone disturbance in the first eight of these conditions is rickets or osteomalacia depending on the age of the patient, and that the disturbance in the next two (chronic-acidosis-or-hyperglycemia and renal rickets) may be osteomalacia or rickets (*vide infra*). The present authors agree that lesions occur in conditions other than osteomalacia which by x-ray somewhat resemble these united but uncalcified fractures seen in osteomalacia. This is especially true in Paget's disease, polyostotic fibrous dysplasia (*osteitis fibrosa disseminata*), and osteogenesis imperfecta. For example, in polyostotic fibrous dysplasia at a point where marked bending has occurred, one often sees by x-ray a somewhat similar appearance (see fig 1), it is quite clear, however, that such a lesion represents a fibrous and cartilaginous union, really a pseudarthrosis, not an uncalcified callus. Furthermore, the fracture-like appearances in most of these other conditions always occur through areas of definite bone pathology by x-ray (see fig 1), in osteomalacia, on the other hand, they may occur in bone appearing otherwise perfectly normal by x-ray. Indeed, the only x-ray evidence of the bone disease may be these "fracture" lines. To be sure, "march fractures" and the "insufficiency fractures" of Hansson (8) occur in otherwise normal appearing bone, such fractures, however, differentiate themselves from the pseudofractures of osteomalacia by uniting and promptly calcifying. Another point of difference lies in the fact that these lines of "fracture" in rickets and osteomalacia tend to be symmetrical and to occur over and over again at certain points,—the necks of the femurs, the ramuses of the pubic and ischial bones, the ribs, etc. Perhaps the commonest of these sites is the axillary edge of the scapula (see fig 2 and fig 37B). In conclusion, therefore, it may be stated that ribbon-like zones of decalcification which occur in otherwise normal appearing bone, which last months or years without regressing, and which exhibit a marked tendency to be symmetrical, occur only in osteomalacia or rickets.

A word should be said about the reason that these united but uncalcified

fractures in osteomalacia and rickets tend to occur in symmetrical positions. This question is discussed in detail by Looser (6) and his explanation is that tensions and stresses are apt to be symmetrical as opposed to trauma, the commonest cause of fractures in general.

The serum chemistry findings in Milkman's Syndrome strongly support its being a form of osteomalacia. As discussed above, with this diagnosis one should find a normal or low serum calcium level (normal circa 10 mg per 100 cc), a low

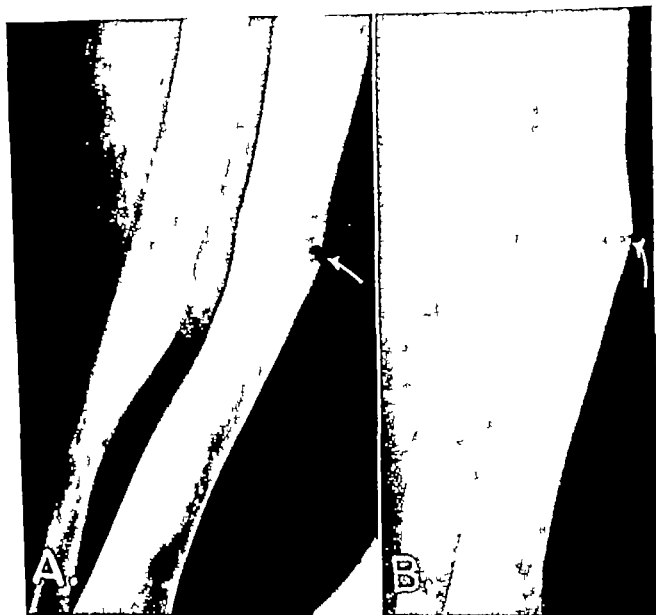


FIG 1 X RAYS OF RIGHT TIBIA ON PATIENT A K #26700 WITH POLYOSTOTIC FIBROUS DYSPLASIA (OSTEITIS FIBROSA DISSEMINATA) TO ILLUSTRATE SIMILARITY IN X RAY APPEARANCE OF PSEUDARTHROSIS (ARROWS) WITH PSEUDOFRACTURES OF MILKMAN (SEE FIGS 2 3 5 AND 6)

(A) on 11-28-38 (B) on 2-2-44

serum phosphorus level (normal circa 3.2 mg for adults, higher for children), and a high serum phosphatase level (normal circa 2-5 Bodansky units (B U) for adults, higher for children). The serum calcium in Milkman's classical case (1, 2), except for one almost certainly faulty determination, was 10-11 mg, the serum phosphorus was very low on two determinations and very high on two others. Since errors in this determination are almost all upward, it is probable that the actual value was low. In the six new cases to be reported below, the blood serum findings were all consistent with osteomalacia, viz: case 1—serum calcium 10.2 and 10.6 mg/100 cc, serum phosphorus 1.6 and 1.5 mg/100 cc,

and serum phosphatase 85 and 76 B U, case 2—serum calcium 87 mg/100 cc, serum phosphorus 10 mg/100 cc, and serum phosphatase 108 B U, case 3—serum calcium 97 and 105 mg/100 cc, serum phosphorus 34 and 32

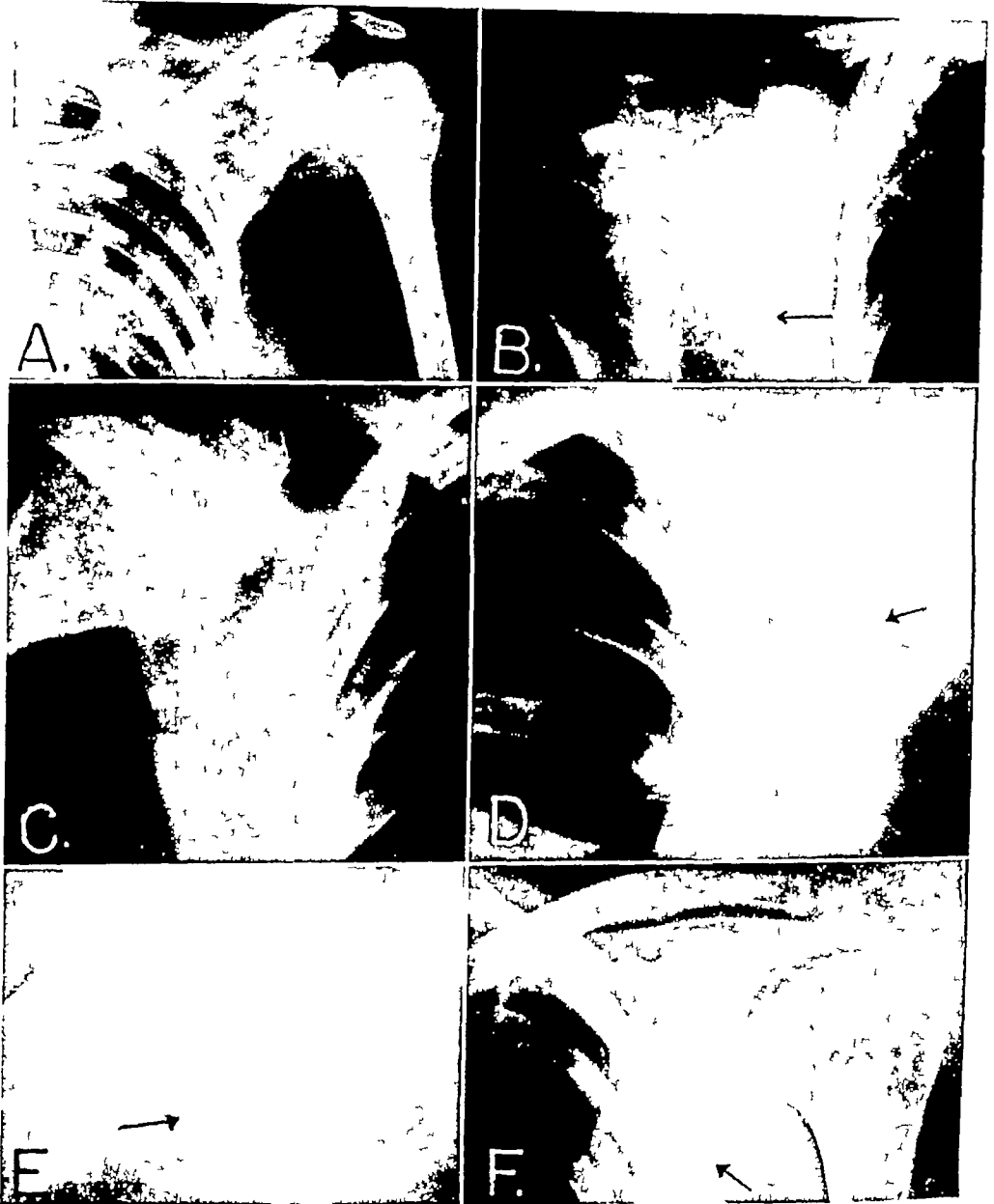


FIG 2 X-RAYS OF SIX DIFFERENT SCAPULAE TO EMPHASIZE FREQUENCY AND UNIFORMITY OF APPEARANCE OF PSEUDOFRACTURES (SEE ARROWS) IN THE SCAPULAE (A) Milkman's case (2), (B) case of Camp and McCullough (7), (C) case 1 right scapula, (D) case 1 left scapula, (E) case 2, and (F) case 4. The authors are indebted to Dr Milkman and the *Journal of Roentgenology* and Dr Camp and *Radiology* for permission to use fig 2A and fig 2B, respectively.

mg/100 cc (blood taken after institution of vitamin D therapy), and serum phosphatase 62 and 94 B U, case 4—serum calcium 95 mg/100 cc, serum

calcium 11.2 and 9.7 mg/100 cc, serum phosphorus 2.2 and 2.2 mg/100 cc, and serum phosphatase 16.3 B U, case 9—serum calcium 9.7 and 10.1 mg/100 cc, serum phosphorus 2.8 and 2.2 mg/100 cc, and serum phosphatase 8.4 and 9.2 B U.

The findings in most of the clear-cut cases of the syndrome reported in the literature which have come to the authors' attention are likewise those of osteomalacia, viz case of Michaels (9), a man of 18, serum calcium 11.6 and 12.7/100 cc, serum phosphorus 1.6 mg/100 cc, case of Debray (10), a woman of 51, serum calcium 10.8 and 11.4 mg/100 cc, serum phosphorus 2.4 mg/100 cc, case of Garcin, Legrand, and Bernard (11), a female of 53 years, serum calcium 10.4 mg/100 cc, serum phosphorus not reported, serum phosphatase 5.5 B U, case of Leedham Green and Golding (12), a 24-year old female, serum calcium 9.6 mg/100 cc, serum phosphorus 2.2 to 2.8 mg/100 cc, and serum phosphatase 30 B U, case of Ravault, Girard, and Didierlaurent (13), female of 61, serum calcium 11.7 mg/100 cc, serum phosphorus 1.0 mg/100 cc, case of Kornblum (14), male, age 25, serum calcium 9.0 and 9.4 mg/100 cc, serum phosphorus 2.5 and 2.1 mg/100 cc, serum phosphatase 5.1 and 6.6 B U, case of Edeiken and Schneeberg (3), female, aged 34, serum calcium 9.3 and 11.0 mg/100 cc, serum phosphorus 2.0 to 2.6 mg/100 cc, serum phosphatase 14.1 and 14.8 B U. On the other hand, the case reported by dall'Acqua, Levi, and Bordoli (15), with a normal serum calcium level, 8.9 mg/100 cc, and a high serum phosphatase level, had a normal serum phosphorus level, 3.4 mg/100 cc. This latter value is to be questioned, however, since these authors found the serum acid soluble phosphorus to be exactly the same as the serum inorganic phosphorus level. Another case in the foreign literature failed to show a low serum phosphorus value, the case of Guillam, Lereboullet and Auzepy (16). It is always possible that the determinations may have been erroneous, it is more probable, however, that some authors by "serum phosphorus" mean "serum acid soluble-phosphorus", or "total serum phosphorus". In the English and American literature "serum phosphorus" has come to be almost synonymous with "serum inorganic phosphorus" and the other determinations are seldom done, this is apparently not so in the French literature. It will be seen, therefore, that the serum calcium, phosphorus and phosphatase values in this group of cases speak strongly in favor of osteomalacia.

The third piece of evidence that Milkman's Syndrome is a form of osteomalacia has to do with the excellent responses one gets to therapies based on the assumption that the syndrome is a form of osteomalacia. Several of the cases reported in the literature have responded favorably to vitamin D therapy, others have not. As will be discussed below, there are several etiologies for osteomalacia and unless one understands just what the etiology is, one cannot obtain the best results. Those cases which are due to simple lack of vitamin D will respond to small doses of this agent; other cases will require other agents in addition. However, the evidence to be presented will make it quite clear that each etiological type of Milkman's Syndrome responds to the correct therapy for overcoming osteomalacia of that particular type.

Why, since bone material has been available to pathologists, does there remain any question as to the nature of the bone disease? Thus, bone biopsy from the case of Michaelis (9) was examined by three eminent German pathologists including Dr Schmorl of Dresden and Dr Pick of Berlin, to be sure, they found the specimen unsatisfactory but they could make no diagnosis other than to rule out myeloma. As mentioned above, two out of three pathologists considered the bone histology of Milkman's classical case to be that of osteomalacia. Dr Granville A. Bennett concurred in the diagnosis of osteomalacia (*vide infra*) making three out of four in favor of this diagnosis. There was also a difference of opinion in the interpretation of the biopsy in case 1 (*vide infra*).

The difficulty in coming to a pathological diagnosis is twofold. A) most of the biopsies have been taken from the pseudofractures, and B) the osteomalacia in many cases is of a low degree. The histology of a callus is very complicated at best, and in a decalcified preparation it is most difficult to differentiate between a callus formed in normal bone and a callus formed in osteomalacic bone. Ham, et al (4) found this out in experimental osteomalacia in rats (*vide supra*). Obviously, in a generalized bone disease such as osteomalacia, one should take one's biopsy away from the fracture site. Even this may not lead to a clear-cut diagnosis, thus, in case 2 such a biopsy failed to show definite osteomalacia. This is perhaps understandable. In the normal adult skeleton, bone formation is not very active, since osteomalacia by definition is a generalized bone condition in which there is a failure of calcium salts to be deposited in newly prepared osteoid, its diagnosis will be more difficult where very little osteoid is being laid down.

Dr Granville A. Bennett of the Department of Pathology of the Harvard Medical School was able to make a definite diagnosis of osteomalacia on a pseudofracture from a rib of case 1 (see fig 3), through the courtesy of Dr Milkman, Dr Bennett also had the opportunity to review the bone histology in his case and came to an almost definite diagnosis of osteomalacia. Excerpts from Dr Bennett's report are here recorded.

"In both cases there is evidence of imperfectly calcified bone matrix in the peripheral portions of the bone trabeculae. This change is more marked in the rib from the California case (case 1) and in this case, at least, seems to indicate osteomalacia. I think osteomalacia must also be considered as the best diagnosis in Milkman's case.

"The other feature of similarity between the two cases is the incorporation of fibrocartilage in the bone trabeculae and in osteoid matrix. In the California case this is best explained, it seems to me, on the basis of imperfect repair of a fracture. In Milkman's case, such metaplastic changes are so frequently seen in close relation to tendon insertions that I wonder if the metaplasia is not the result of reparative proliferation, in an unstable osteomalacic bone."

An inspection of fig 3 will leave no doubt as to the diagnosis of osteomalacia in this case. Furthermore, the bone tissue obtained at autopsy on Case 9 shows florid osteomalacia (see fig 38). Thus, we have, as a fourth piece of evidence that Milkman's Syndrome is a form of osteomalacia, the histological findings



*Case 1* Diagnosis Milkman's syndrome, osteomalacia of undetermined etiology It was this case which first brought Milkman's Syndrome to the attention of one of us (F A) The patient has never been seen by our Boston group but all the data have been supplied by a group of California investigators to whom the present authors are greatly indebted \*

The patient Mrs A J first consulted Dr Smith in 1939 at the age of 37 Following the birth of her second child 7 years previously she developed 'tiredness of the hips' pain in the back and difficulty in picking up her heels " The condition progressed so that in 1939 she could walk only with crutches and had great difficulty getting up from a sitting position

The points of interest in the past history were jaundice at 22 of short duration absence of dental trouble, poor appetite, regular bowel movements occasional digestive disturbances relieved by food or alkalis and nocturia (three times)



FIG 3 MILKMAN'S SYNDROME CASE 1 X RAY OF PSEUDOFRACTURE OF RIB  
For microscopic appearance see fig 4

Physical examination was non-contributory except for weight of 112½ pounds, deformities of the back and chest suggesting collapsed vertebrae, limitation of motion of the hip joints, white sclerae and blood pressure of 120/80

As regards the x ray findings (see fig 5 and 6), the following quotations are taken from Dr Stone's report of 9-21-36 "in almost all of the bones the number of trabeculae is decreased in many places, particularly in the ribs there are streaks of decreased density which closely resemble fractures one would need to consider these all as fractures were it not for the fact that in some places such as the scapulae and the pelvis they do not completely cross the bone the periosteum overlying these areas of decreased density has been

\* This group includes the late Dr Arthur M Smith of Oakland California who in 1940 first wrote one of us (F A) concerning the patient Dr Dudley W Bennett of the University of California Hospital San Francisco who studied the patient extensively in 1937 and whose findings were transmitted to the authors Dr Robert S Stone and Dr Earl R Miller of the University of California Hospital who made the x rays of the patient available Dr Fred Erick C Bost who took a biopsy of one of the ribs and Dr Charles L Connor of the University of California Hospital San Francisco who sent the biopsy material on for study by Dr Cranville A Bennett

elevated, and in many places subperiosteal new bone has been laid down the changes seen are almost bilaterally symmetrical thus we find that there is an area of this osteoid

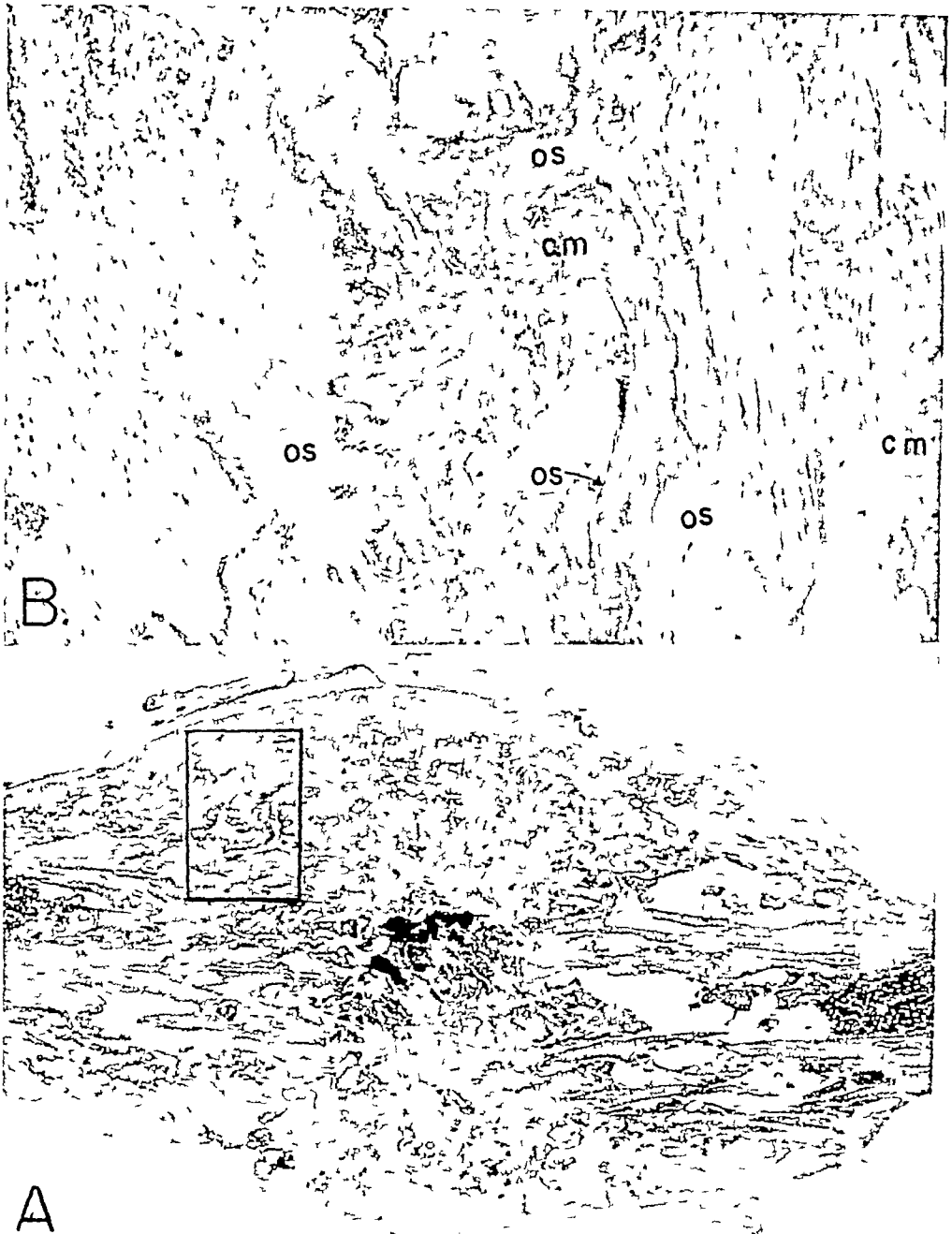


FIG 4 MILKMAN'S SYNDROME CASE 1 PSEUDOFRACTURE OF RIB

(A) Low-power magnification of section through pseudofracture of rib (see fig 3)  
 (B) High-power magnification of same In "B" note large amount of osteoid (os) which contrasts itself very clearly from the calcified matrix (cm) The authors are indebted to Dr Granville A Bennett for these histological sections

tissue resembling fracture on the axillary border of the right scapula about two inches below the glenoid, whereas it is only about one inch below the glenoid on the left scapula (see fig 2C and fig 2D) extending laterally from both sacroiliac joints into the respective

ilea are short lines of the pseudofracture type on June 19, 1935 patient was examined for suspected fracture of the left hip and a line closely resembling a fracture line was seen in the middle of the neck the necks of the femurs (later films) have become more slender and the heads have bent around this, in its completed stage as seen at the present date, resembles bilaterally slipped epiphyses "



FIG 5 MILKMAN'S SYNDROME CASE 1 X RAY TAKEN 9-18-37 SHOWING PSEUDOFRACTURES (ARROWS) IN BOTH ULNAE

The authors are indebted to Dr Robert S Stone for these x rays

The following laboratory studies taken while she was under the care of Dr Dudley W Bennett in 1936 are of interest serum calcium 10.7 mg/100 cc serum phosphorus 2.5 mg/100 cc serum protein 7.44 gm/100 cc blood creatinine 1.2 mg/100 cc urinary calcium excretion, while on a low calcium intake 0.007 gm/24 hours (very low) serum phosphatase high on one determination and normal on the next

Subsequent studies in October 1937 showed serum calcium 10.2 and 10.6 mg/100 cc, serum phosphorus 1.6 and 1.5 mg/100 cc, serum phosphatase 8.6 and 7.6 Bodansky units, and urinary calcium excretion 0.018 gm/24 hours In October 1941 the following serum

determinations were made at the Samuel Merritt Hospital in Oakland, California sodium chloride 600 mg /100 cc , content of  $\text{CO}_2$  59.3 volumes per cent



FIG 6 MILKMAN'S SYNDROME CASE 1 X-RAYS OF PELVIS TAKEN ON 6-19-35 (A) AND 9-16-37 (B)

In "A" note normal texture of bones except for "pseudofractures" (arrows) X-rays furnished by Dr Robert S Stone

A biopsy of one of the pseudofractures of the ribs was performed March 6, 1940 by Dr Bost The pathological diagnosis made by Dr Granville A Bennett was osteomalacia (see above)

The chemical findings,—normal serum calcium, low serum phosphorus, and high serum phosphatase—were consistent with osteomalacia, the x rays were those of Milkman's Syndrome, a biopsy was diagnosed osteomalacia, there was little to suggest disorder of fat-soluble vitamins other than vitamin D, the serum chemistry was not that of renal acidosis, accordingly, it was advised that the patient take large doses of vitamin D starting with 900,000 units daily. This therapy was started in February 1942. In one month she noticed marked improvement and by September 1943 was able to report that the pain was gone and that the bones and muscles were much stronger. She had taken vitamin D continuously, but the exact amounts are not available.

#### MILKMAN'S SYNDROME VS ORDINARY OSTEOMALACIA

What is so peculiar to Milkman's Syndrome that it should be separated from osteomalacia in general? The answer to this question, in the authors' opinion, is the co-existence of the pseudofractures and a skeleton which otherwise is not definitely abnormal as judged by x-rays. When Dr Arthur M Smith of Oakland, California sent the x rays and case history on case 1 (vide supra) to one of us, he (F A) could not believe, in spite of the fact that the serum chemistry was that of osteomalacia, that the underlying pathology could be that in the absence of generalized demineralization by x ray early in the disease at a time when pseudofractures were already present (see fig 6A). The pseudofractures, of course, are likewise seen in cases with extensive generalized demineralization. The authors believe, therefore, that there is no sharp line of demarcation between Milkman's Syndrome and classical osteomalacia, that the differences are quantitative rather than qualitative, but that the term Milkman's Syndrome should be retained as an x ray diagnosis to call attention to the fact that one can have an underlying osteomalacia when the only x ray evidence is the ribbon-like zones of decalcification.

#### THE FOUR DEGREES OF OSTEOMALACIA

It is possible to separate cases of osteomalacia into four degrees with respect to their severity: 1) chemical-osteomalacia-with normal phosphatase, 2) chemical-osteomalacia with high phosphatase, 3) Milkman's Syndrome, and 4) advanced osteomalacia. The first degree of osteomalacia takes in those cases where there has arisen a disproportion of the serum calcium in relation to the serum phosphorus such that calcium is not deposited in newly formed osteoid, but where this disorder has not yet led to sufficient weakness of the skeleton as a whole to bring about an increased production of osteoblasts and hence a high serum phosphatase level. The second degree of osteomalacia takes in those cases where the condition has progressed to the point of stimulating osteoblastic activity but not to the extent of causing pseudofracture or obvious demineralization, and where clinical or x ray evidence of bone disease is lacking. The third degree takes in those cases with chemical osteomalacia and pseudofractures but without obvious generalized demineralization. The fourth degree is reserved for those cases with out-and-out bone disease.

#### DIGRESSION ON ACTION OF PARATHYROID HORMONE

It is almost impossible to discuss any aspect of calcium metabolism without introducing the mode of action of the parathyroid hormone. The administration

of parathyroid hormone is followed by four cardinal metabolic changes: an increase of calcium in the serum, a decrease of phosphorus in the serum, an increase of calcium in the urine, and an increase of phosphorus in the urine. If one assumes that the four cardinal metabolic changes are interrelated phenomena, which almost certainly must be the case, the most plausible sequence of events which one would arrive at, even without experimentation, is that the initial effect is an increased excretion of phosphorus in the urine, that this leads to a low serum phosphorus level, that this leads to increased pulling of calcium and phosphate ions into the serum from the bones or gut, that this results in an elevation of the serum calcium level, and finally that this leads to an increase in the amount of calcium in the urine (see fig 7). There is considerable experimental data to support the above sequence of events. Albright and Ellsworth (17) found that the administration of parathyroid extract was immediately (within one hour)

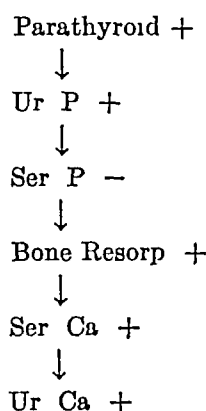


FIG 7 SEQUENCE OF ADJUSTMENTS TO PARATHYROID HORMONE

followed by a phosphate diuresis and that this preceded the other sequelae. Harrison and Harrison (18) showed that parathyroid hormone decreases the re-absorption in the kidney tubules of the phosphorus of the glomerular filtrate.

There is one more point about parathyroid physiology which must be brought out since use of it will be made later on,—namely, the thesis that the stimulus for parathyroid function is a low serum calcium level. All conditions which tend to decrease the serum calcium level are associated with hyperplasia of parathyroid tissue, viz a low calcium diet (Marine (19), Luce (20)), pregnancy (Kehrer (21)), osteomalacia and rickets and lack of vitamin D (Erdheim (22), Ritter, (23), Pappenheimer and Minor (24), Higgins and Sheard (25), and Albright, Butler, and Bloomberg (26)), kidney disease with phosphate retention (Pappenheimer and Wilens (27)), and parenteral administration of phosphates in rabbits (Drake, Albright, and Castleman (28)). That a high serum phosphorus level is not a stimulus to parathyroid hyperplasia is shown by the fact that in osteomalacia and rickets, where the parathyroids are hyperplastic, the serum phosphorus is usually low.

The possibility that the parathyroid hormone acts directly on bone in addition to its action on phosphate excretion by the kidney cannot be denied. This is discussed in a paper by Ingalls, Donaldson, and Albright (29).

## DIGRESSION ON ACTION OF VITAMIN D

A knowledge of the action of vitamin D is paramount to an understanding of the new data to be presented below. As a result of previous studies in this clinic some theories have been advanced (Albright and Sulkowitch (30)). In figures 8, 9, 10 and 11 certain of the data of these studies are again presented, this time in chart form. Before this and other material are examined it should be noted that, in order to unravel the action of vitamin D, it is necessary to study its effects on parathyroidless individuals, otherwise, one runs into the danger of considering as primary sequelae of the action of vitamin D changes which are secondary to an alteration in the activity of the parathyroid glands. There are 7 points from these previous studies which the authors would like to underline.

*Point 1* the starting-off point of any discussion of the action of vitamin D is the repeatedly demonstrated fact that its administration decreases the fecal calcium and phosphorus excretions. This was clearly shown by Bauer, Marble, and Claflin (32) in 1932 (see fig. 12) and is also well demonstrated in fig. 8 in metabolic periods 8 to 10, in fig. 9 in metabolic periods 10 through 13, and in fig. 10 in metabolic periods 15 to 20. But this is not enough, one would like to know whether the changes in calcium metabolism are due to changes in phosphorus metabolism or vice versa, whether the decreased fecal excretions are due to increased absorptions from the gut or decreased re-excretions into the gut, etc. It is necessary, therefore, to explore these studies further.

*Point 2* an increase in calcium in the diet increases the calcium in the feces and this in turn increases the phosphorus in the feces, on the other hand, an increase of phosphorus in the diet has very little effect on the fecal phosphorus excretion or on the fecal calcium excretion. These facts were well brought out in studies on a patient with vitamin D resistant rickets (see fig. 8). When the calcium in the diet was increased (see metabolic periods 3 through 5) there was a definite increase in the fecal calcium and phosphorus excretions, on the other hand, when the phosphorus which had previously been given intravenously was administered by mouth in period 10, there was no increase in the fecal phosphorus excretion or in the very low fecal calcium excretion. Illustrative of the same point are the data of Gargill, Gilligan, and Blumgart (33) recharted in fig. 13 (q v) on a patient with osteomalacia. Note especially that the fecal phosphorus was not increased in periods 21 to 24 when the phosphorus intake was increased fivefold. It should be noted that these findings are merely confirmatory of previous findings by Nicolaysen (34) on rats.

As a corollary to points 1 and 2 it follows that vitamin D decreases the fecal phosphorus excretion through its effect on the fecal calcium excretion. This corollary was likewise arrived at by Nicolaysen (34) in his studies on rats.

*Point 3* the decreased fecal calcium excretion with vitamin D is the result of increased calcium absorption from the gut and not of decreased calcium excretion into the gut. For the studies to demonstrate this (see fig. 9), a patient with idiopathic hypoparathyroidism with a low serum calcium level was chosen so that calcium given intravenously would not immediately appear in the urine.

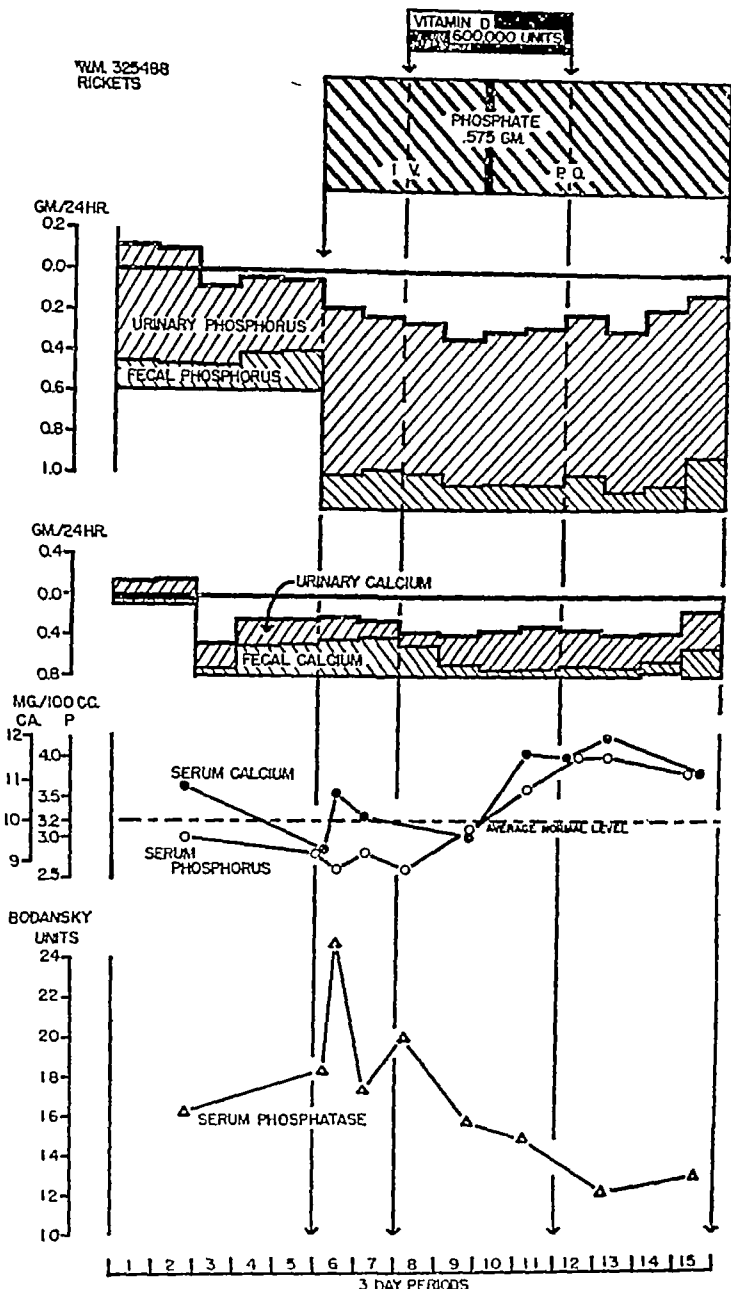


FIG 8 METABOLIC DATA ON PATIENT (W M #325488) WITH VITAMIN D-RESISTANT-RICKETS

Metabolic data in this and later figures are arranged according to the following scheme. There is a horizontal base line, intake is charted on a reverse scale downwards from this base line, the fecal and urinary excretions are then measured from the intake line upward toward the base line. If the output (feces and urine) exceeds the intake the final level will be above the base line, if it does not, the final level will be below the base line. Thus a positive balance will be indicated by a clear area below the base line, a negative balance by a shaded area above the base line. The scales for the nitrogen\*, phosphorus, and calcium data are so chosen that fluctuations in any one balance should be accompanied by equal fluctuations in the sum of the other two balances provided that the changes in nitrogen balance represent changes in body protoplasm ( $N:P$  equals 14:1), and changes in calcium balance represent changes in calcium deposited in bone ( $Ca:P$  equals 8:1), and the changes in phosphorus balance represent either changes in body protoplasm or in the amount of calcium in the skeleton.

The chart is self-explanatory. The points discussed in the text are: the rise in fecal calcium and phosphorus excretions following an increase in calcium intake (see periods 3 through 5), the failure of the fecal phosphorus excretion to rise when phosphorus was administered intravenously (see periods 6 through 9) or by mouth (see periods 10 and 11), the fall in fecal calcium and phosphorus excretions following administration of vitamin D (see periods 8 through 11), the failure of intravenous phosphorus to elevate the serum phosphorus (see periods 6 and 7), and the rise in serum phosphorus without an increased urinary phosphorus excretion following administration of Vitamin D (see periods 8 to 11). Recharted from Albright and Sulkowitch (30).

\* In this particular study the nitrogen data are not included



PR. 4636  
HYPOPARATHYROIDISM

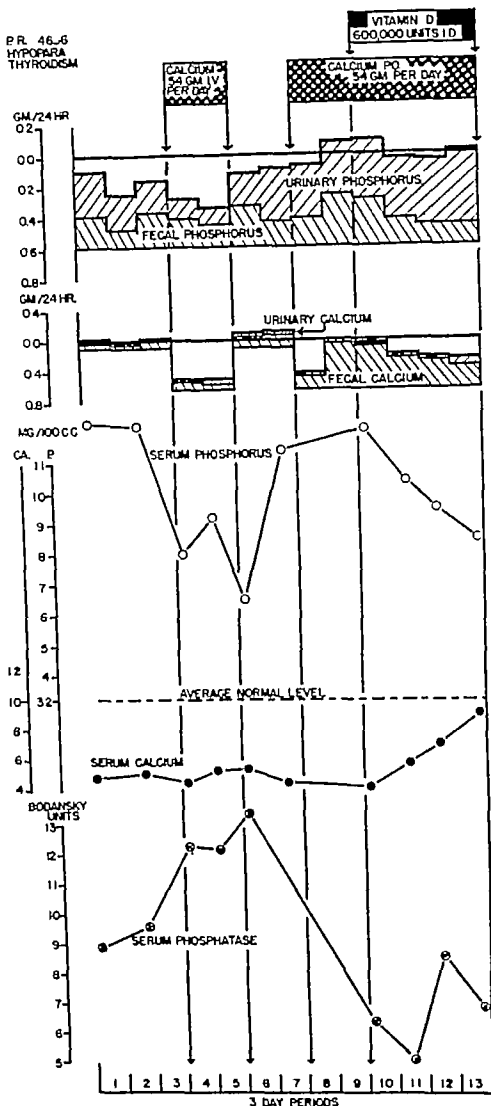


FIG 9 METABOLIC DATA ON A PATIENT (P R. #4636) WITH IDIOPATHIC HYPOPARATHYROIDISM

For construction of figure see paragraph in *italics* under fig 8

The figure is self-explanatory. The points emphasized in the text are the failure of calcium administered intravenously to increase the urinary or fecal calcium excretions (see periods 4 and 5), the marked rise in fecal calcium and phosphorus excretions when the same amount of calcium was administered by mouth (see periods 8 through 10), the fall in fecal calcium and phosphorus excretions following administration of vitamin D (see periods 10 through 13), and the failure of the serum calcium to rise when calcium was given intravenously (see periods 4 and 5) as opposed to the definite rise in serum calcium following vitamin D (see periods 10 through 13) although the calcium balance was 5 than in periods 10 through 13. Recharted from Albright and S. 71

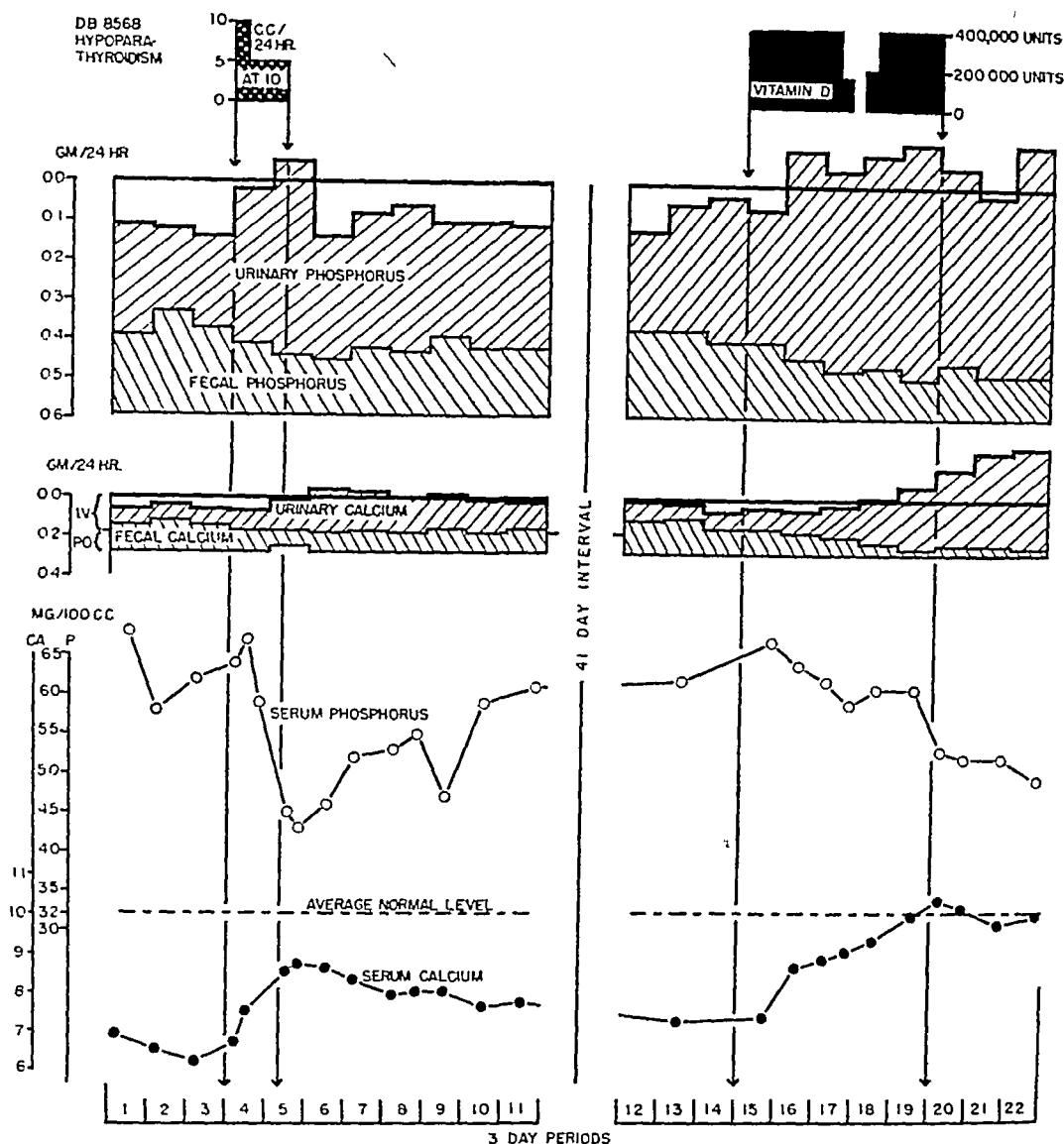


FIG 10 METABOLIC DATA ON A PATIENT (D B #8568) WITH IDIOPATHIC HYPOPARATHYROIDISM

For explanation of construction of chart see paragraph in italics under fig 8

The chart is self-explanatory. Note that more than one-half the calcium intake was given intravenously. Note the fact that the urinary excretions of calcium and phosphorus as the result of vitamin D administration (see periods 15 through 22) increased more than the fecal excretions decreased, thus leading to negative calcium and phosphorus balances, the fact that the sequelae following administration of dihydrotachysterol (A T 10) were qualitatively the same as those following vitamin D but quantitatively different in that the ratio of the phosphorus-excretion-effect to the calcium-absorption-effect was greater with dihydrotachysterol than with vitamin D, and the fact that the serum phosphorus level fell more with dihydrotachysterol for any degree of elevation of serum calcium than it did with vitamin D. Not commented upon but of interest was the failure of the serum calcium level to rise above normal following vitamin D therapy (period 20 to 22), although the serum phosphorus continued to fall and the serum calcium excretion increased at an accelerated rate. Recharted from Albright, Bloomberg, Drake, and Sulkowitch (31).

In fig 9 it will be noted that when 540 mg of added calcium daily were administered intravenously during metabolic periods 4 and 5, there was no appreciable change in fecal calcium excretion. Later on (period 8) when the same amount of

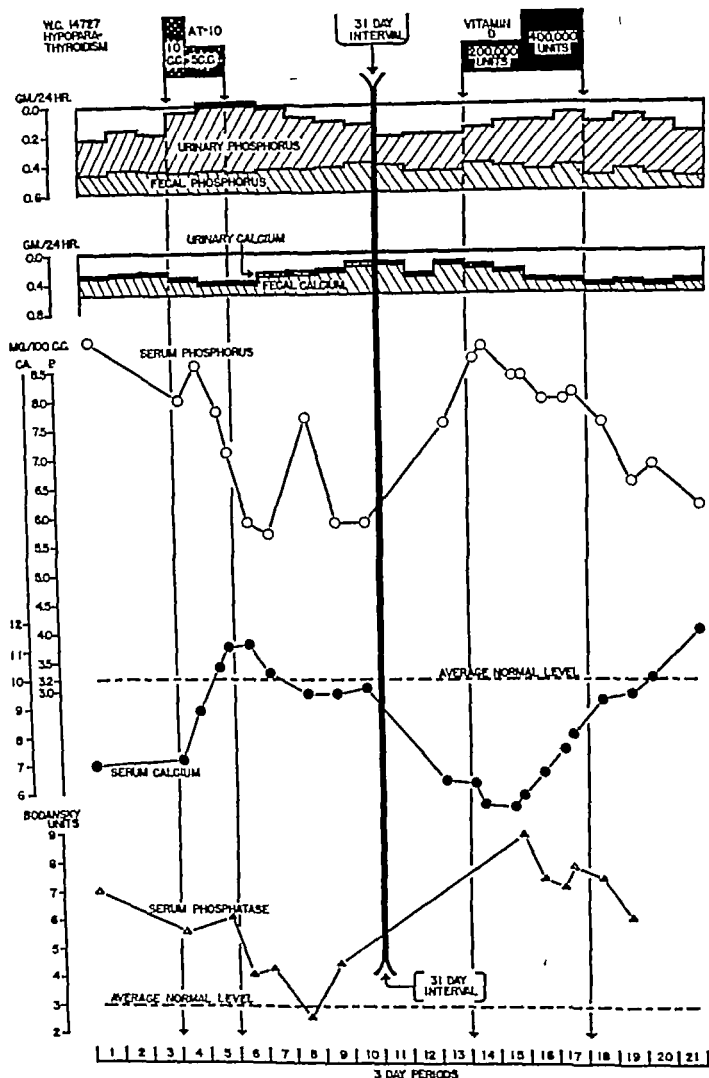


FIG 11 METABOLIC DATA ON PATIENT (W C #14727) WITH IDIOPATHIC HYPOPARATHYROIDISM RECHARTED FROM ALBRIGHT, BLOOMBERG, DRAKE, AND SULKOWITZ (31) TO CONTRAST THE EFFECT OF DIHYDROTACHYSTEROL WITH THAT OF VITAMIN D

For explanation of construction of chart see paragraph in *italics* under fig 8

Note, as in fig 10, that the serum phosphorus level for any given rise in serum calcium level is lower with dihydrotachysterol (A.T 10) than with vitamin D

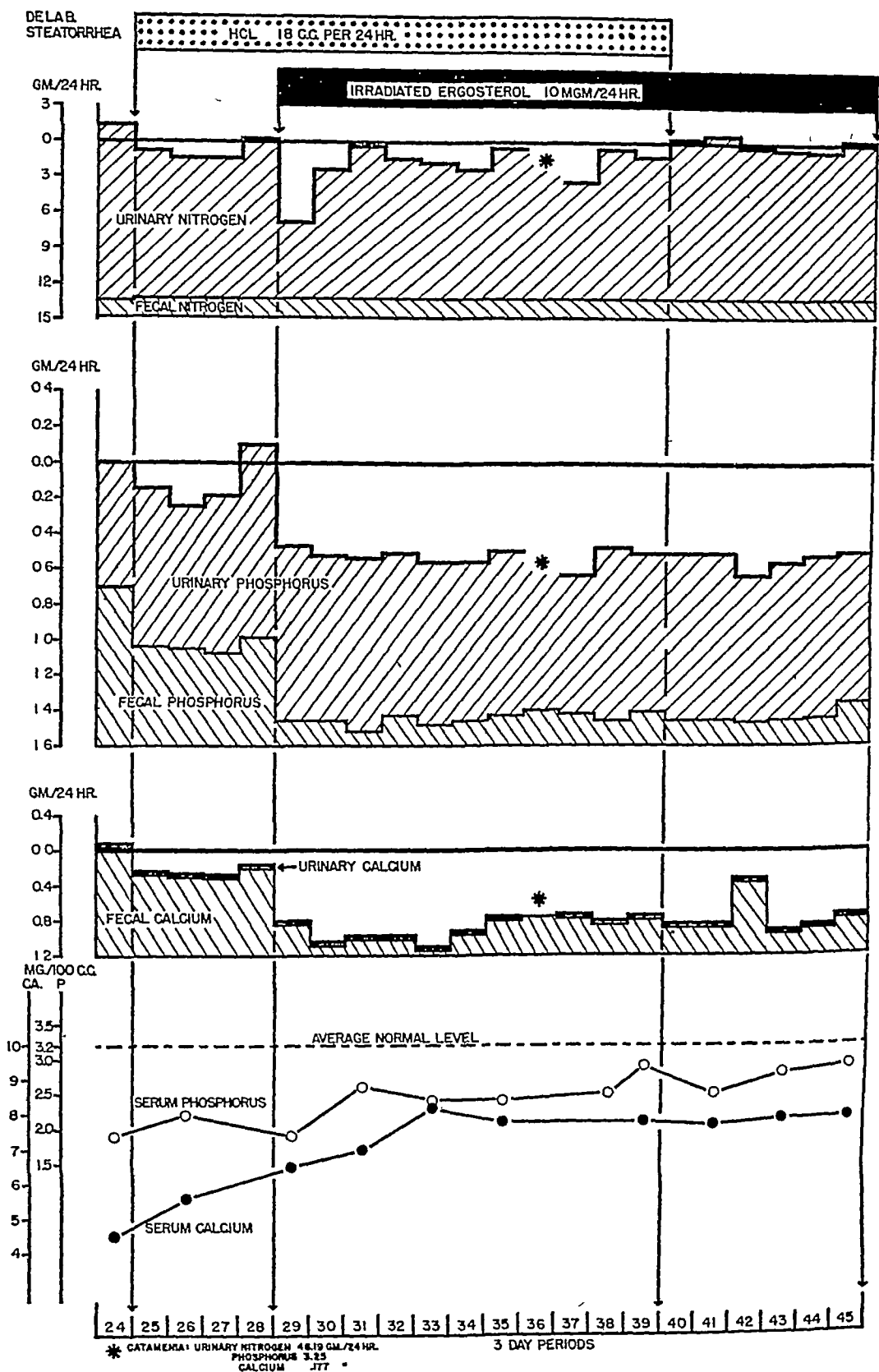


FIG 12 EFFECT OF VITAMIN D ON NITROGEN, PHOSPHORUS AND CALCIUM METABOLISMS IN A PATIENT WITH OSTEOMALACIA SECONDARY TO STEATORRHEA

For construction of chart see paragraph in italics under fig 8

Note low urinary calcium excretion throughout and markedly decreased fecal phosphorus and fecal calcium excretions upon administration of vitamin D in period 29. Diagram constructed from data of Bauer, Marble, and Clafin (32) with permission of the authors and the Journal of Clinical Investigation

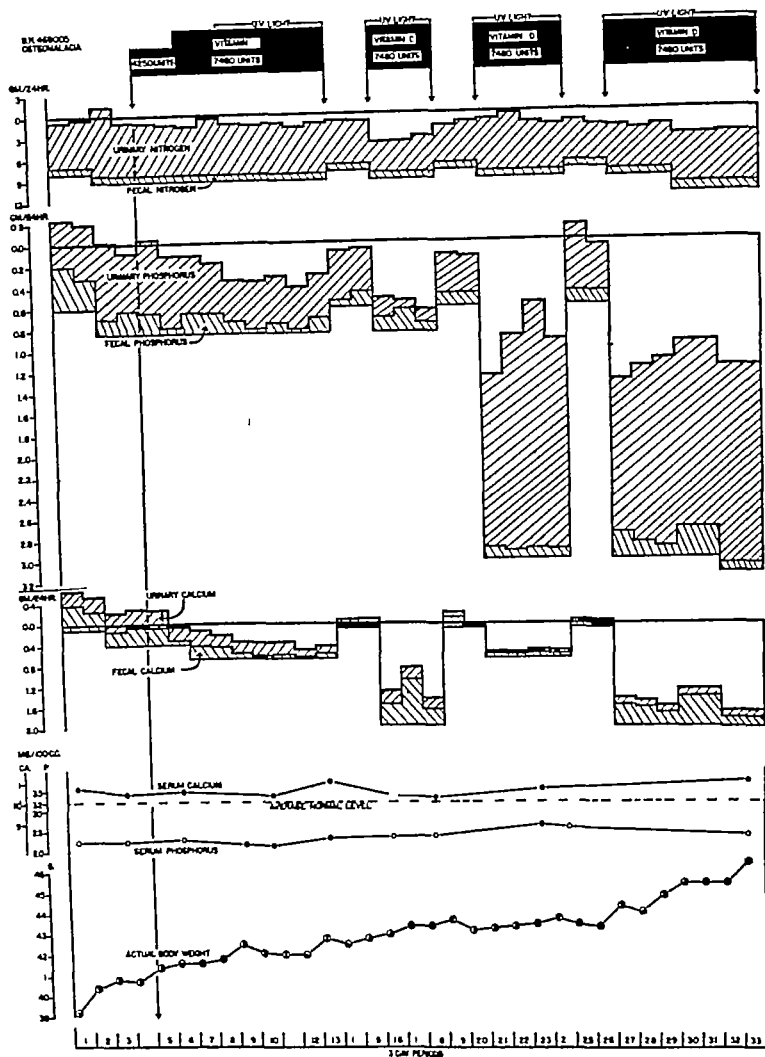


FIG 13 METABOLIC STUDIES ON PATIENT WITH OSTEOMALACIA OF QUESTIONABLE ETIOLOGY  
—POSSIBLY IDIOPATHIC HYPERCALCAEMIA

For construction of diagram see paragraph in italics under fig 8

The points emphasized in the text are large amount of calcium in the urine in spite of severe osteomalacia, decrease in fecal calcium and phosphorus on administration of vitamin D (see periods 5 through 14) lack of effect of phosphorus intake on fecal phosphorus excretion (compare periods 22-25 with periods 26-27), and parallelism between fecal calcium excretion and fecal phosphorus excretion (compare periods 22-25 with periods 27-31). Recharted from Gargill, Gilligan, and Blumgart (33) with permission from the Archives of Internal Medicine.

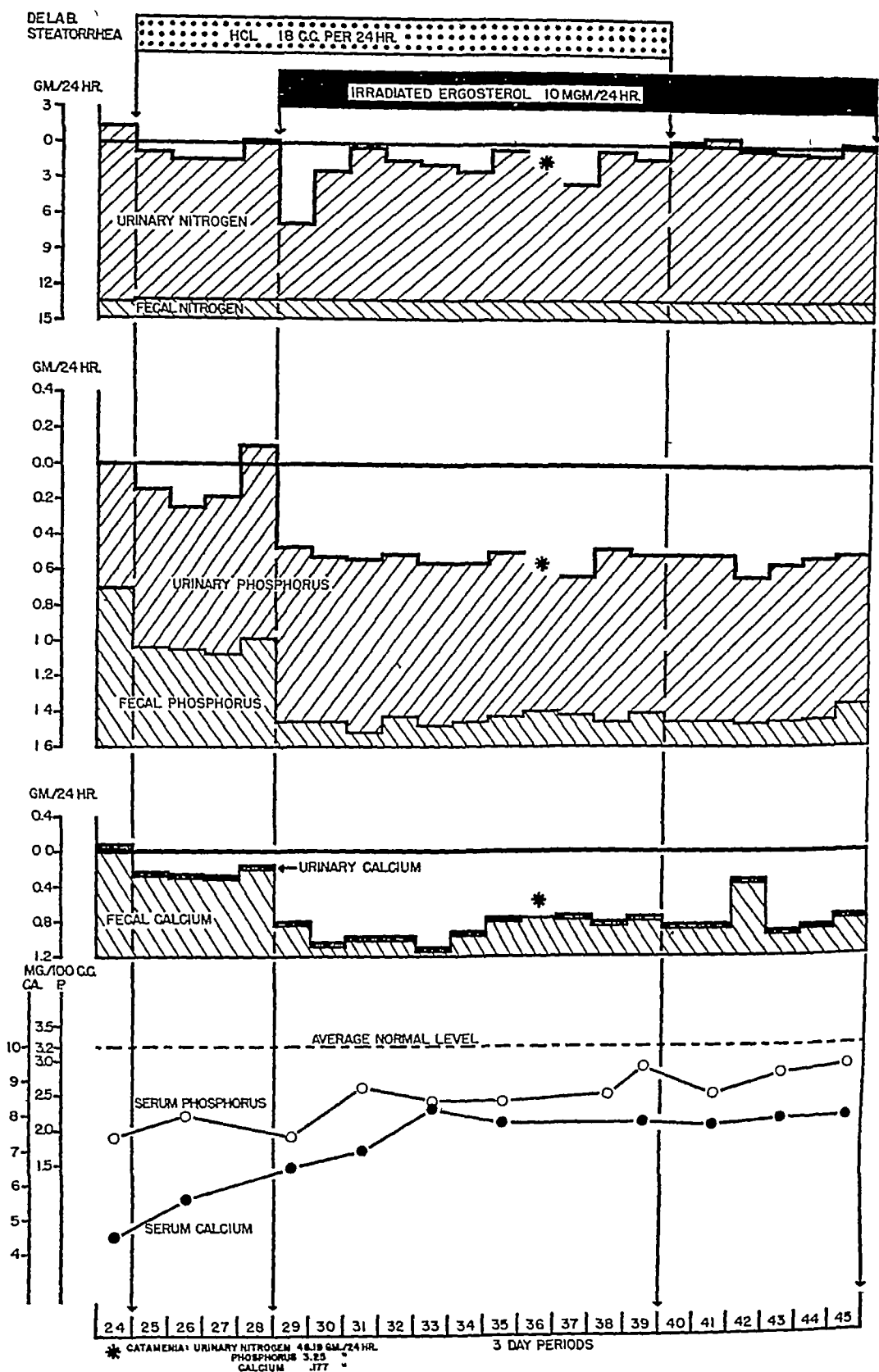


FIG 12 EFFECT OF VITAMIN D ON NITROGEN, PHOSPHORUS AND CALCIUM METABOLISMS IN A PATIENT WITH OSTEOMALACIA SECONDARY TO STEATORRHEA

For construction of chart see paragraph in italics under fig 8

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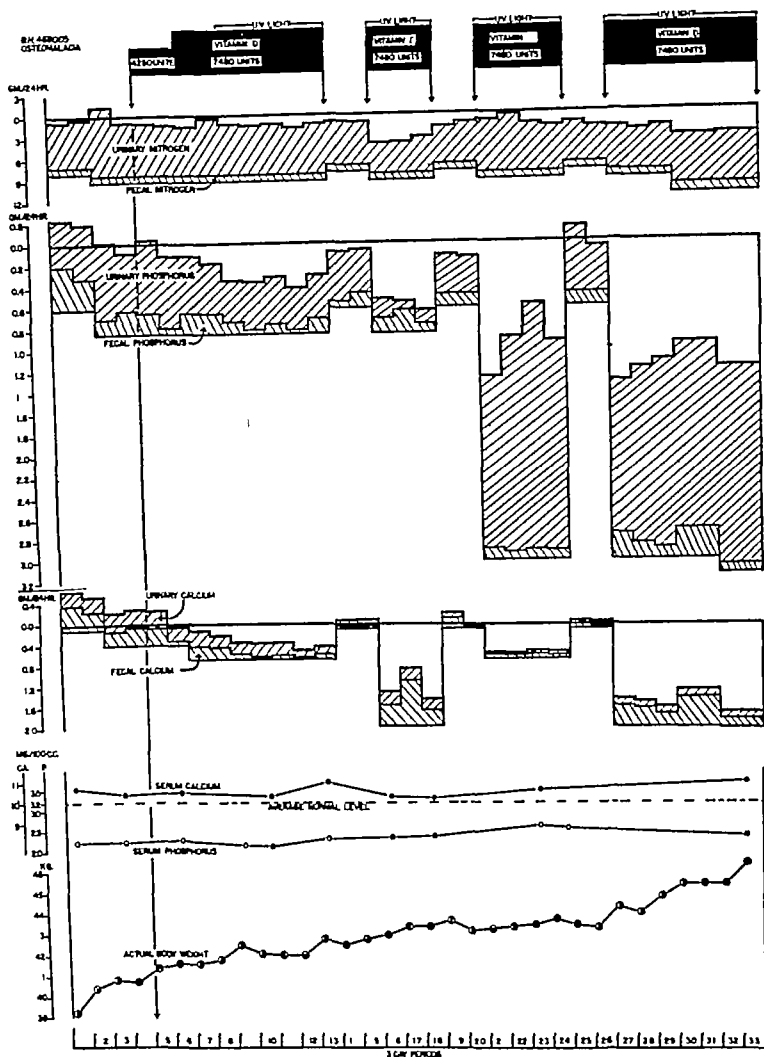


FIG 13 METABOLIC STUDIES ON PATIENT WITH OSTEOMALACIA OF QUESTIONABLE ETIOLOGY  
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For construction of diagram see paragraph in *italics* under fig 8

The points emphasised in the text are large amount of calcium in the urine in spite of severe osteomalacia, decrease in fecal calcium and phosphorus on administration of vitamin D (see periods 5 through 14) lack of effect of phosphorus intake on fecal phosphorus excretion (compare periods 22-25 with periods 26-27), and parallelism between fecal calcium excretion and fecal phosphorus excretion (compare periods 22-25 with periods 27-31) Recharted from Gargill, Gilligan, and Blumgart (33) with permission from the Archives of Internal Medicine

calcium was given by mouth, there was a marked increase in the fecal calcium excretion. Now when vitamin D was administered in period 10 the fecal calcium excretion showed a definite decrease. Thus, since it had already been shown that the giving of almost all of the calcium intravenously did not result in any increase in the amount of calcium appearing in the feces, this decrease of calcium in the feces with vitamin D could not have been due to decreased calcium re-excretion into the gut, one cannot decrease something which is non-existent. These findings are in agreement with those of Hannon, Liu, Chu, Wang, Chen, and Chou (35), who found that calcium chloride administered intravenously was retained in osteomalacia which suggested that the high fecal calcium excretion in that condition is the result of lack of calcium absorption and not of increased re-excretion.

*Point 4* the increased calcium absorption from the gut partly explains—at least in patients with osteomalacia or rickets—the rise in serum calcium level and the increase in urinary calcium excretion which follow vitamin D therapy. The importance of the modifying adverb, “partly”, will appear below. This rise in serum calcium level and urinary calcium excretion with vitamin D therapy is well shown in fig. 8, metabolic periods 8 to 11.

*Point 5* the rising serum phosphorus level following the administration of vitamin D is to be attributed only slightly, if at all, to the increased phosphorus absorption from the gut, but mostly to decreased parathyroid activity resulting from the rise in serum calcium level. Thus, to refer again to fig. 8, if increased phosphorus absorption was the cause of the rising serum phosphorus level with vitamin D administration (see metabolic periods 8 through 11) the serum phosphorus should have risen during periods 6 and 7 when a large amount of the phosphorus was given intravenously. Such was not the case in spite of the fact that the urinary phosphorus excretion during periods 6 and 7 did increase markedly. On the other hand, when vitamin D was administered the serum phosphorus rose with no appreciable change in the urinary phosphorus excretion. Thus in metabolic period 6 with a serum phosphorus level of 2.7 mg/100 cc he excreted 2465 mg of phosphorus in the urine, whereas in period 13 with a serum value of 4.0 mg/100 cc he excreted 2376 mg in the urine. This lack of increase in the urinary phosphorus excretion in the presence of a rising serum phosphorus level is most suggestive of a decrease in the activity of the parathyroid glands and in the authors' opinion is so to be interpreted. This point of view gains weight from the fact that when one administers vitamin D to parathyroidless individuals the serum phosphorus level does not rise (*vide infra*).

*Point 6* whereas all the sequelae to the administration of vitamin D so far mentioned are attributable, in the authors' opinion, to the increased calcium absorption from the gut, there are other sequelae which make it necessary to hypothesize a second equally fundamental action of vitamin D, namely to cause an increased urinary phosphorus excretion. In the first place, it was shown by György (36) that massive doses of vitamin D cause decalcification, it would be hard to explain decalcification if the only action of vitamin D were increased calcium absorption. This second action of vitamin D is well brought out in



fig 10 which shows studies on a patient with idiopathic hypoparathyroidism. It will be noted that during the administration of large doses of vitamin D (metabolic periods 15 through 19) the fecal calcium excretion fell, the serum calcium level rose, the urinary calcium excretion rose, all of which were to be expected, but! the urinary calcium excretion rose more than the fecal calcium excretion fell so that the patient went into a strongly negative calcium balance! The explanation is to be seen in the phosphorus metabolic data. With vitamin D administration the urinary phosphorus excretion rose more than the fecal phosphorus excretion fell and the serum phosphorus level fell. It would seem that vitamin D in large doses has an effect on phosphorus metabolism similar to the parathyroid hormone and that, as discussed elsewhere (Albright and Sulkowitch (30)), this effect of vitamin D on phosphorus excretion in the urine is entirely separate from its action on calcium absorption from the gut. That the increased phosphorus excretion in the urine following vitamin D administration is not a sequela of the increased calcium absorption is shown in fig 9 where the intravenous administration of calcium (periods 4 and 5) was followed by a decreased rather than an increased urinary phosphorus excretion.

A second piece of evidence that the two actions of vitamin D are independent of each other lies in the studies of Albright, Bloomberg, Drake, and Sulkowitch (31) from which they concluded that dihydrotachysterol, a substance very similar to vitamin D, has the same two actions but in a different ratio, one to the other, it was their conclusion that dihydrotachysterol has more phosphorus-excretion-effect per unit of calcium-absorption-effect than vitamin D (see figures 10 and 11). It should be noted in figs 10 and 11 that the serum phosphorus level following administration of dihydrotachysterol (AT 10) was lower for any level of serum calcium than following the administration of vitamin D.

In patients with their parathyroids intact the second effect of vitamin D, to increase the urinary excretion of phosphorus, may be entirely masked by the first effect. Thus, the sequence of events,—increased calcium absorption, rising serum calcium, decreased parathyroid activity, depressed urinary phosphorus excretion, rising serum phosphorus level—, results in the opposite effect on the phosphorus metabolism, hence, whether the serum phosphorus goes down or up with vitamin D administration will depend on which effect of vitamin D predominates. Since one cannot decrease parathyroid activity in parathyroidless individuals, the urinary phosphorus excretion must rise and the serum phosphorus level must fall with vitamin D administration in such individuals (see figs 9, 10, and 11).

*Point 7* the rising serum calcium level following the administration of vitamin D to a normal or hypoparathyroid individual is to be attributed to the urinary-phosphorus-excretion-effect and not to the calcium absorption-effect of vitamin D. Fig 9 is most instructive as regards this point. When 540 mg daily of calcium were administered intravenously to the patient with idiopathic hypoparathyroidism (metabolic periods 4 and 5) there was a marked fall in the serum phosphorus level and in the urinary phosphorus excretion, but no rise in the serum

calcium level, evidently calcium phosphate was formed and deposited somewhere, possibly in the bones, possibly in the reticulo-endothelial cells. Quite different were the sequelae to the administration of vitamin D (see periods 10 through 13). There, instead of a fall in the urinary phosphorus excretion there was a rise, the serum phosphorus level fell as it did following administration of calcium intravenously, but the serum calcium level rose in spite of the fact that the positive calcium balance resulting from the decreased fecal calcium excretion was less than the positive balance resulting from the intravenously administered calcium. It is quite clear from these observations that, to raise the serum calcium level in the hypoparathyroid individual, and the same is probably true of the normal, it is necessary that space be made, as it were, by the removal of phosphate so that more calcium can be dissolved in the body fluids. In the patient with osteomalacia or rickets, on the other hand, where the body fluids are depleted as regards calcium and phosphate ions, the increased absorption of calcium resulting from vitamin D will lead to a rise in serum calcium level (*vide supra*).

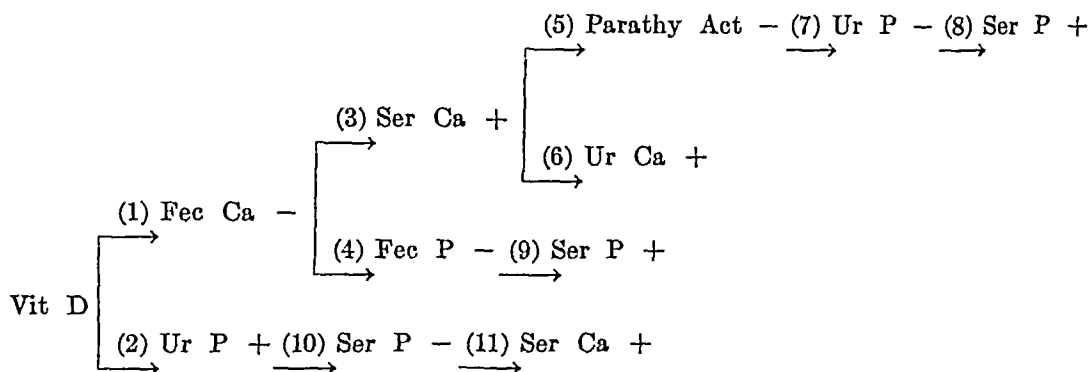


FIG 14 DIAGRAM TO ILLUSTRATE METABOLIC SEQUELAE OF VITAMIN D ACTION

It follows from the above discussion that the phosphorus-excretion-effect of dihydrotachysterol or of vitamin D and not the calcium-absorption-effect is the significant property of these substances in the treatment of hypoparathyroidism, the converse is true in the treatment of osteomalacia. Thus, dihydrotachysterol would seem to be the better agent in the treatment of hypoparathyroidism and vitamin D the better agent in the treatment of osteomalacia.

In fig 14 the two actions of vitamin D and the various sequelae of each action are summarized in diagrammatic form. It will be noted that whether the serum phosphorus rises (arrow 8) or falls (arrow 10) will depend on whether the first action of vitamin D (arrow 1) or the second action of vitamin D (arrow 2) predominates, and that in parathyroidless individuals arrows 5, 7, and 8 drop out. A diagram for dihydrotachysterol would be the same except that arrows 2, 10, and 11 would be increased in size.

With respect to the serum calcium and phosphorus findings it is possible to divide cases of osteomalacia into three types: a) those in which compensatory over-activity of the parathyroids is lacking, b) those where there is compensatory over-activity of the parathyroids sufficient to maintain the serum calcium at a normal level, and c) those where there is compensatory overactivity of the para-

thyroids but where this is insufficient to maintain the serum calcium at a normal level. In the first type, the serum calcium would be low and the serum phosphorus normal, in the second the serum calcium would be normal and the serum phosphorus low, and in the third the serum calcium and the serum phosphorus would both be low.

This dual action of vitamin D, which has been proposed, is not out of harmony with the findings of Harrison and Harrison (18) who studied factors influencing re-absorption of phosphorus from the kidney tubules. They showed that the parathyroid hormone decreases re-absorption and that vitamin D, in rachitic animals only, increases re-absorption. It seems likely that the increased re-absorption with vitamin D is due to a secondarily decreased parathyroid activity, the experiment should be repeated on parathyroidectomized animals in which case the present authors would predict a decrease in phosphate re-absorption in the tubules.

It would appear from the above discussion that dihydrotachysterol holds an intermediate position between vitamin D and the parathyroid hormone (see table below)

	Calcium absorption	Phosphorus urinary excretion
Vitamin D	++++	++
Dihydrotachysterol	++	+++
Parathyroid hormone	+	++++

In fig. 15 some data, re-charted from Albright, Sulkowitch, and Bloomberg (37) bring into contrast the metabolic effects of vitamin D, dihydrotachysterol, and the parathyroid hormone

#### ETIOLOGIES OF OSTEOMALACIA MET IN THE UNITED STATES

##### Classification

- A) Vitamin D lack,
  - a) 'Simple' vitamin D lack
  - b) Resistance to vitamin D
  - c) Steatorrhea
- B) Renal Acidosis,
  - a) Tubular insufficiency without-glomerular insufficiency
  - b) Fanconi Syndrome
- C) Idiopathic Hypercalcaemia
- D) Hyperparathyroidism with Osteitis Fibrosa Generalisata during transitional stage following removal of parathyroid tumor

#### OSTEOMALACIA RESULTING FROM "SIMPLE" VITAMIN D LACK

By the expression, "osteomalacia resulting from simple vitamin D lack", the authors have in mind a condition like the usual variety of infantile rickets where the bone disease is responsive to small doses of vitamin D. It is appreciated, of course, that in a case of osteomalacia which is curable by small amounts of vitamin D there may be other contributing factors such as lack of exposure to sunlight, lack of calcium and phosphorus in the diet, etc. Indeed, the patient

not appreciably lowered by 150,000 units of vitamin D for nine days and by 300,000 units of vitamin D for an additional three days A third metabolic study

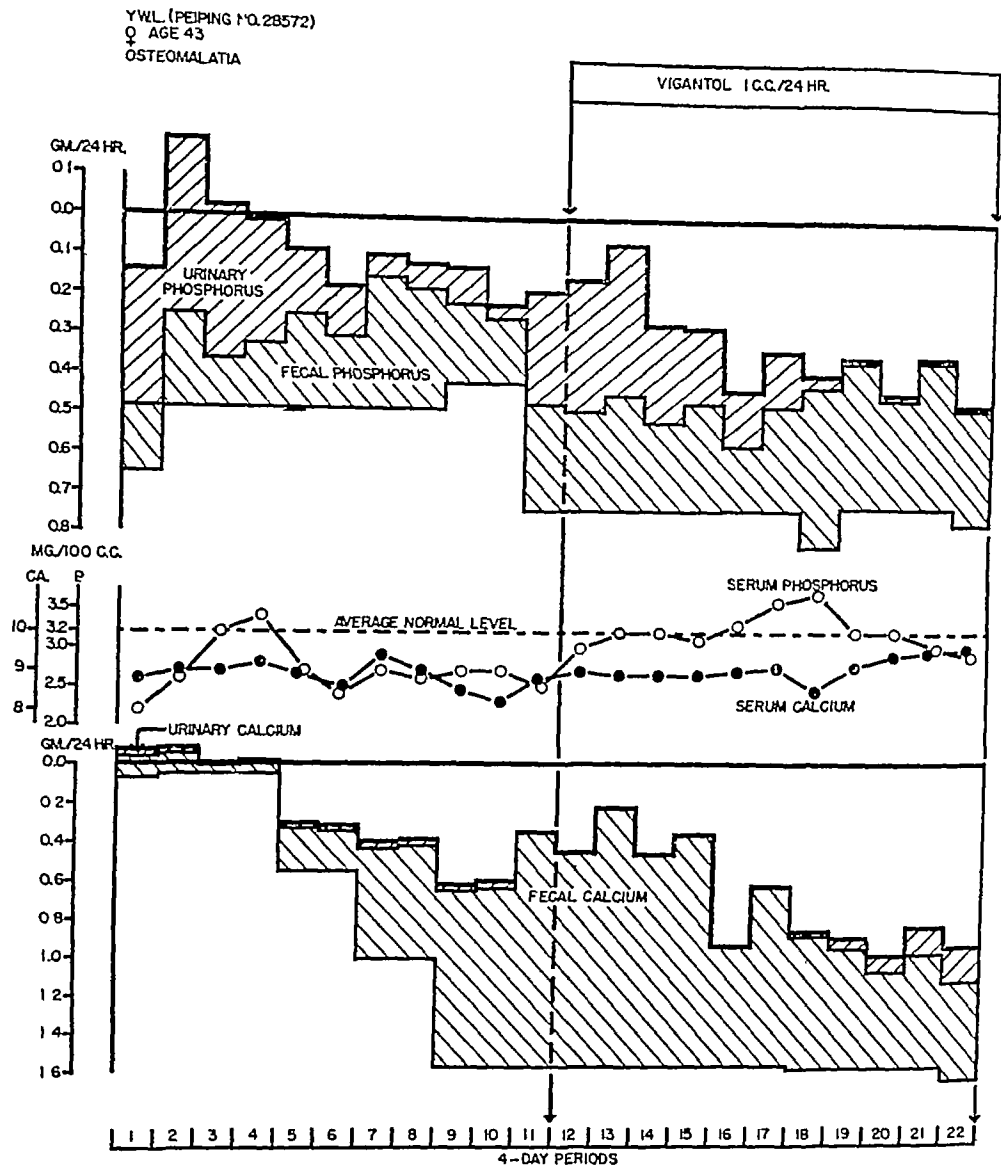


FIG 16 METABOLIC STUDY ON PATIENT WITH OSTEOMALACIA AS IT OCCURS IN CHINA  
For construction of chart see paragraph in italics under fig 8

Figure 18 is self-explanatory Note especially extremely low urinary calcium excretion until period 19, marked fall in urinary phosphorus excretion with rising serum phosphorus during periods 11 through 18, rise in urinary calcium excretion when urinary phosphorus excretion becomes negligible which indicates that calcium cannot be retained without phosphorus (see periods 19 through 22), and the strongly positive calcium and phosphorus balances even before administration of the vitamin D preparation, Vigantol These pre-medication positive balances are probably to be attributed not only to the high calcium intake but to the vitamin D content of the experimental diet Recharted from Liu et al (39) with permission of Dr R. R. Hannon and the Chinese Medical Journal

on this same patient is shown in fig 8 where it will be seen that 600,000 units of vitamin D daily caused a definite decrease in fecal calcium in six days For contrast, note the rapid decrease in fecal calcium excretion in a study on a patient with osteomalacia associated with steatorrhea during the first three days of a

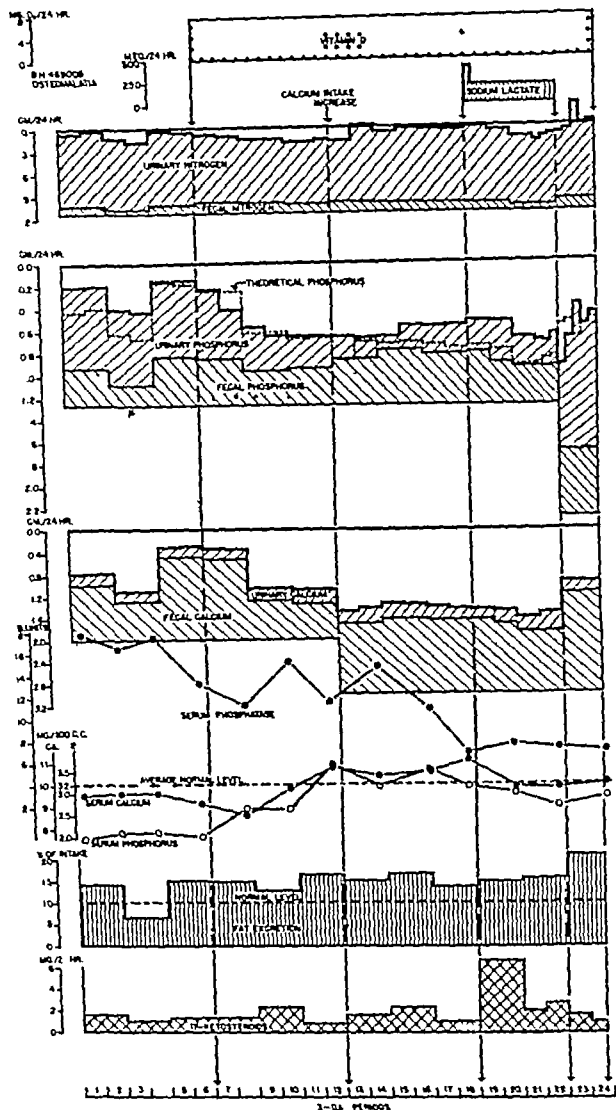


FIG 17 METABOLIC STUDY ON PATIENT WITH OSTEOMALACIA RESULTING FROM IDIOPATHIC HYPERCALCAEMIA

For construction of chart see paragraph in italics under fig 8

Subject of this experiment carried out in 1945 at the Massachusetts General Hospital was the same patient studied by Gargill et al (33) in 1930. The figure is self explanatory. Note especially the strongly positive calcium balance during the pre medication periods (1 through 6) which suggests that the hospital diet contained more calcium or more vitamin D or more of both than the diet which the patient received at home. Note the relatively high and rather constant urinary calcium excretion in this patient with marked osteomalacia, note as in fig 16 the rising serum phosphorus level with the falling urinary phosphorus excretion on administration of vitamin D which combination of findings suggest decreased parathyroid activity, and note the falling serum phosphatase level after a continued positive calcium balance. Attention is called to the lack of effect of sodium lactate administration (period 19 through 23) on the calcium balance which is strong evidence that the hypercalcaemia is not due to some form of acidosis. This study will be more pertinently discussed in a later paper.

relatively small dose of vitamin D (see fig 12, period 29) In the second study in fig 15 on the patient with vitamin D resistant rickets it should be noted in passing that the fecal calcium excretion decreased markedly in the first three days of treatment with 12.5 mg daily of dihydrotachysterol (10 cc of AT 10), this, of course, was a massive dose so one cannot conclude that this patient is nonresistant to dihydrotachysterol

It was the belief of Albright et al (26) that wherever vitamin D has its primary action, in that place in this patient there existed a resistance to the action of vitamin D, it was not their conception that this patient suffered from some endogenous error in calcium or phosphorus metabolism, such as idiopathic hypercalcuria (*vide infra*), which would necessitate increased calcium absorption and hence more vitamin D to prevent a negative calcium balance

This patient has been carefully followed to see what would happen to the disordered calcium and phosphorus metabolism when the patient ceased growing In fig 18 are charted the serum calcium, phosphorus, and phosphatase values in relation to his age, height, and vitamin D therapy This chart is a continuation of that shown in fig 8 in the paper by Albright et al (26) It will be seen that growth ceased about January 1939 at the age of  $18\frac{1}{2}$  years and that vitamin D was omitted in February 1940 It will be further noted that, although the patient has remained symptom free and able to work at a war job, the serum phosphorus level has continued low and the serum alkaline phosphatase level high during the five years since the omitting of vitamin D His epiphyses being now united, his diagnosis becomes "chemical-osteomalacia-with-high-phosphatase"

There is one feature of this much-studied patient with so-called vitamin D resistant rickets which might make one somewhat question such a simple explanation He has had a tendency at times to put out more calcium in the urine than one would expect in an individual with rickets due to vitamin D lack, thus, when first studied at the age of twelve at the Children's Hospital at a time when his rickets was active, he put out, before receiving vitamin D therapy, 40 mg of calcium daily in the urine on an intake of 760 mg This excretion is not high for a normal child but is high for a patient with active rickets due to vitamin D lack The later metabolic studies are mostly complicated by the fact that he had received vitamin D at rather short intervals before the onset of the observations, the low urinary calcium excretions in the first experiment in fig 15 are probably to be attributed to a recent parathyroid exploration However, a 24-hour urine collected in 1945 after four years off vitamin D contained only 81 mg of calcium and the authors conclude that the disorder is best explained by an abnormal resistance to the action of vitamin D

#### HYPOVITAMINOSIS D SECONDARY TO STEATORRHEA

Perhaps the commonest form of hypovitaminosis D in adults is where the primary difficulty is a steatorrhea Vitamin D, being fat-soluble, is not absorbed, the same holds for other fat-soluble vitamins Therefore, such patients differ from the others in that they have, in addition to hypovitaminosis D,

deficiencies in the other fat-soluble vitamins, notably K, A, and perhaps E (Albright and Stewart (40))

The two chief causes of steatorrhea in this country are 1) an idiopathic steatorrhea which masquerades under the diagnosis of non-tropical sprue or in children, coeliac disease or Gee's disease, and 2) chronic pancreatitis. The latter differs from the former in several respects: the duodenal contents are markedly deficient in pancreatic ferments, a larger percentage of the fat in the stools is in the form of neutral fats as opposed to fatty acids and soaps, meat fibers are often

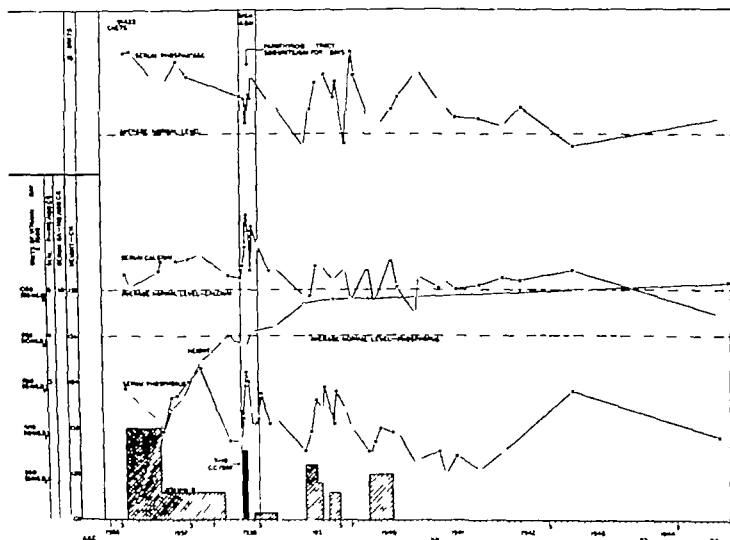


FIG 18 EFFECT OF MATURATION OF SKELETON (CESSATION OF GROWTH) ON SERUM CALCIUM PHOSPHORUS AND PHOSPHATASE LEVELS IN A PATIENT WITH VITAMIN D RESISTANT RICKETS  
For further discussion see text

present in the stools and the fecal nitrogen excretions are increased, the glucose tolerance is normal rather than increased, normal gastric acidity rather than hypoacidity is the rule. A third cause of steatorrhea is insufficiency of the small intestine resulting from any one of a number of causes, often some short-circuiting operation, in the case reported by Albright and Stewart (40) the small intestinal insufficiency was the result of terminal ileitis plus several operative procedures.

The diagnosis of osteomalacia secondary to steatorrhea often remains unrecognized for a long period of time, especially in those cases where diarrhea is not a prominent feature. Thus case 2 underwent a gallbladder exploration because it was not recognized that the pain in her right upper quadrant was due to a fractured rib, she then masqueraded under the diagnosis of Marie-Strumpel arthritis

because some thoiatrast, introduced into the sub-arachnoid space in an attempt to find a ruptured disc as the cause of her symptoms, deposited itself on the dura (see fig 19) and was mistaken for calcified ligaments, finally, x-rays taken to evaluate the degree of arthritis showed the characteristic findings of Milkman's Syndrome and the correct diagnosis was arrived at. As so often is the case, once suspected the diagnosis offers no difficulties. The serum carotinoid and vitamin A contents should be decreased and the prothombin time increased. A fecal fat

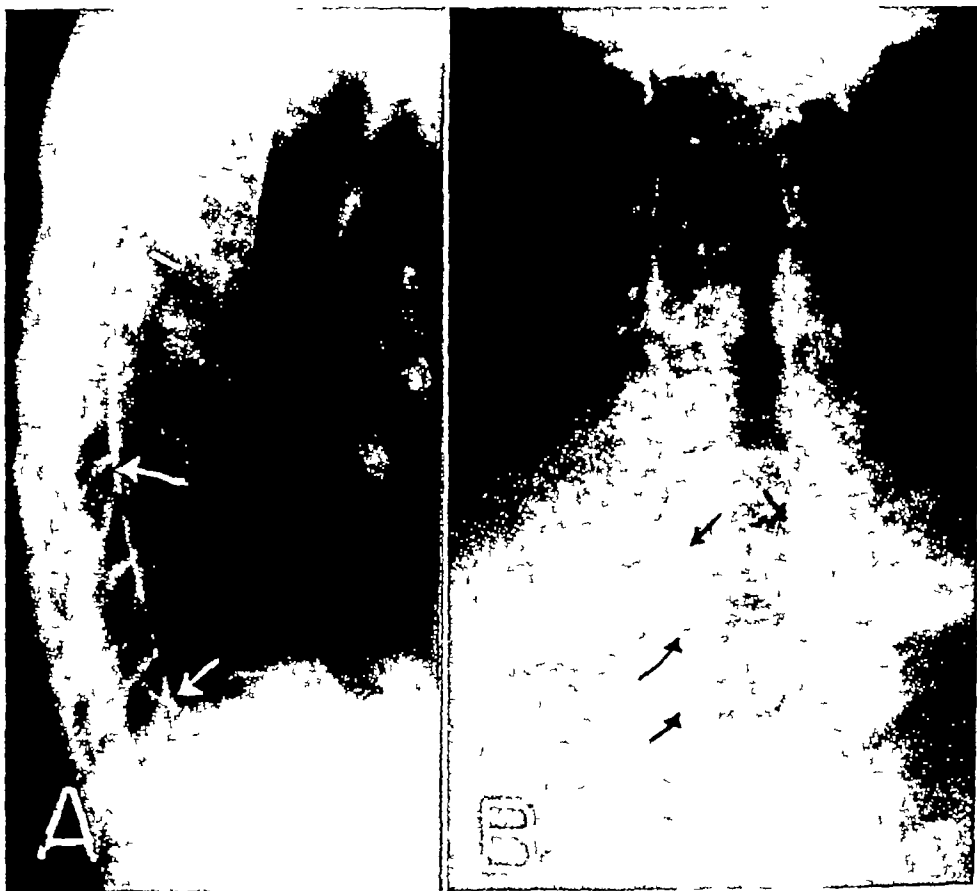


FIG 19 CASE 2, X-RAYS TO SHOW IMPREGNATION OF DURA WITH THORATRAST (SEE ARROWS)

(A) Lateral view of thoracic vertebrae, (B) anterior posterior view of cervical and upper thoracic vertebrae. Note in "B" impregnation of dural sheaths of spinal nerves as they leave spinal column.

value over ten per cent of the intake or over twenty-five per cent of the dried fecal weight is strongly suggestive of steatorrhea. The characteristic blood chemistry findings of osteomalacia (vide supra) should be present. A number of the cases (e.g. case reported by Bauer, Marble, and Claflin (32)) have had, instead of a low serum phosphorus and a relatively normal serum calcium level, a normal serum phosphorus level and a low serum calcium level with tetany. Presumably in such cases there has been no compensatory hyperplasia of the parathyroids (vide supra).



The treatment consists in correction of the steatorrhea if possible as by the administration of crude liver extract in the case of non-tropical sprue. If this is not possible, a low fat diet should be prescribed and the fat-soluble vitamins should be given in large amounts between meals so that they escape being dissolved in what little fat is present. The most important thing is not to forget to give all the fat-soluble vitamins rather than just the one, the lack of which is causing the most impressive symptoms. Thus, in case 2, it was not until large amounts of vitamin E in the form of alpha tocopherol were given that the patient's strength returned.

**Case 2** Diagnoses steatorrhea (non tropical sprue), hypovitaminosis D, K, A, and E, osteomalacia (Milkman's syndrome), thoratrast impregnation of dura.

Mrs E M, #395554, a housewife of thirty, first entered the Massachusetts General Hospital as a patient of Dr William A Rogers on March 5, 1943 because of generalized skeletal pain. Her first symptoms started 12 years previously, shortly after her first and only pregnancy, when she noticed pain in her feet while walking on rocks while stream fishing. Later she noticed easy fatigability and for about two years girdle pains in her mid-trunk region. Although she tended to be constipated, she did admit of episodes of diarrhea at which time her stools were very bulky. She lost from her best weight of over 100 pounds down to 73 pounds.

Because of the pain in the right hypochondrium she underwent a gallbladder operation but no abnormality was found.

Her past history was irrelevant except for an appendectomy 10 years previously and a thyroidectomy for non toxic adenoma 7 years previously.

On February 11, 1942 she received thoratrast intraspinally in an effort to demonstrate a ruptured disc none was demonstrated.

On physical examination she was exceedingly weak, she was unable to raise her head off the pillow. Her ribs were very tender, her abdomen was distended and showed very little peristalsis. There was a muddy-brown pigmentation of her face such as is seen in pregnancy. The pigmentation also involved the creases of her hands and the gallbladder scar but not the appendix scar.

Laboratory studies: urine normal, haemoglobin 14.0 gm/100 cc, white count 4,800, sedimentation rate normal, Hinton test for syphilis negative, phenolsulphonphthalein excretion excellent, stools negative except for moderate amounts of fat mostly in the form of fatty acids. The chemical analysis of the serum showed 7.3 gm of protein, 8.7 mg of calcium, 1.0 mg of phosphorus 10.8 Bodansky units of alkaline phosphatase, 18.0 mg of non protein nitrogen, 108 mg of total cholesterol per 100 cc and 103.0 m eq of chloride, 19 m eq of  $\text{CO}_2$  content (24.0 m eq in a repeat determination), and 144.0 m eq of sodium per liter. The 17 ketosteroid excretion and the rate of growth of axillary hair were within normal limits. As evidence of vitamin K deficiency she had a prolonged prothrombin time, 33 seconds as compared with the normal of 22 seconds, as evidence of vitamin A deficiency, she had a decreased amount of vitamin A in her blood, 0.4 units per cc (normal equals 1.5 units per cc), and no carotinoids. Her gastric acidity was normal, the creatinine excretion was very low (487 mg/24 hours), while the creatine excretion was high (662 mg/24 hours). Liver function tests were normal. Pancreatic ferments were found to be normal in the duodenal contents by Dr Martin M Nothmann of the Pratt Diagnostic Hospital to whom the authors are very much indebted.

X rays showed impregnation of the entire dura of the cord and brain with thoratrast (see fig 10). Generalized decalcification was thought to be present, and the lamina dura about the teeth was absent. The left second and third metatarsal bones showed united uncalcified fractures, there were multiple similar fractures of the ribs: one in the ascending ramus of the right pubic bone, one in the descending ramus of the left ischium and finally

one in the left scapula (see fig 2E) The x-rays also demonstrated marked hypo-peristalsis of the small bowel with puddling

The diagnoses made were non-tropical sprue, hypovitaminosis with respect to all the fat-soluble vitamins, and osteomalacia with Milkman's Syndrome Accordingly, she was treated with large amounts of the four fat-soluble vitamins, a low fat diet, desoxycholic acid, and liver extract (at first a pure preparation but later, on advice from Dr Edward Kepler of the Mayo Clinic, a crude preparation) On this therapy her united but uncalcified fractures promptly calcified, her vitamin A level and prothrombin time returned to normal, but she continued to be very weak. Testosterone propionate was administered, 25 mg three times a week, with some improvement in strength and reduction of creatine excretion to zero After 7 weeks of therapy and 4 weeks of testosterone injections, her vitamin E dosage was changed from 2 cc of wheat germ oil daily by mouth to 25 mg of alpha tocopherol three times daily This change was attended by a most dramatic increase in body strength She continued to be distended, however For this she was given acetyl-beta-methyl-choline-chloride (Mecholyl), 10 mg intramuscularly three times a day with marked relief On discharge from the hospital two and one-half months after onset of therapy, her serum calcium was 9.9 mg /100 cc, her serum phosphorus had returned to normal, 3.3 mg /100 cc, and her serum phosphatase was still above normal, 14.0 Bodansky units

The patient was last seen in July 1944 She had done quite well on the whole However, x-rays still showed poor peristalsis and the carotinoid content of the blood remained negligible, indications that the underlying pathology was still present A later gastric analysis had shown no free hydrochloric acid even after histamine She had now no skeletal symptoms but continued to show a chemical osteomalacia, her last blood values being serum calcium 9.2 mg /100 cc, serum phosphorus 3.6 mg /100 cc, and serum alkaline phosphatase 10.4 Bodansky units

*Case 3* Diagnoses steatorrhea (non-tropical sprue), hypovitaminosis D, osteomalacia (Milkman's syndrome)

Sister F, a fifty-year old nun, #415754, was referred in August 1943 by Dr Joseph Ferrucci of Framingham, Massachusetts because of generalized skeletal pains, generalized demineralization by x-ray, and a pseudofracture of the shaft of one femur (see fig 20A) She volunteered that the skeletal symptoms tended to come on every spring and improved during the summer Since June 15, 1943 she had been taking 10,000 units of vitamin A, 1,000 units of vitamin D, and 4 grams of calcium gluconate daily, and felt markedly improved

In her past history it is of interest that she was treated for anemia and leucopenia in July 1934 A gastric analysis at that time showed some free hydrochloric acid Her anemia responded to liver extract and iron In 1938 she developed generalized anasarca, thought at that time to be of cardiac origin, but there was no orthopnea, there is no record of a serum protein determination having been done She was still anemic at that time, and she gradually improved under digitalis and iron therapy Her catamenia had ceased two years previously

Laboratory studies stools showed meat fibers and increased amounts of fat, a gastric analysis revealed no free hydrochloric acid even after histamine injection, routine urine analysis negative, urine concentrated to 1.020 after 1 cc of pituitrin subcutaneously, red count 3.7 million, haemoglobin 10.5 gm /100 cc, white count 3,400, phenolsulphonphthalein excretion excellent, serum calcium 9.7 and 10.5 mg /100 cc, serum phosphorus 3.4 and 3.2 mg /100 cc, serum alkaline phosphatase 6.2 and 9.4 B U, urinary calcium excretion very low, 17 mg /24 hours, serum protein 6.8 gm /100 cc, serum CO<sub>2</sub> combining power 24 m eq /liter, serum chloride 102 m eq /liter, prothrombin time normal, blood vitamin A and carotenoid contents normal (at a later date) Dr Martin M Nothmann of the Pratt Diagnostic Hospital found the pancreatic ferments to be normal in the duodenal contents He also found normal blood lipase and diastase levels.

The x rays still showed some generalized decalcification but the lamina dura around the remaining teeth was intact, the pseudofracture in the left femur had entirely healed (see fig 20B)

With the generalized demineralization the pseudofracture by x ray, and the high serum phosphatase level it was clear that this patient was suffering from osteomalacia. The absence of a low serum phosphorus level was ascribed to that fact that she was convalescent, presumably due to the vitamin D and sunlight with healing osteomalacia, the serum calcium and phosphorus values return to normal before the serum phosphatase level (cf case 2). It was felt that the cause of the osteomalacia was undoubtedly steatorrhea. In this

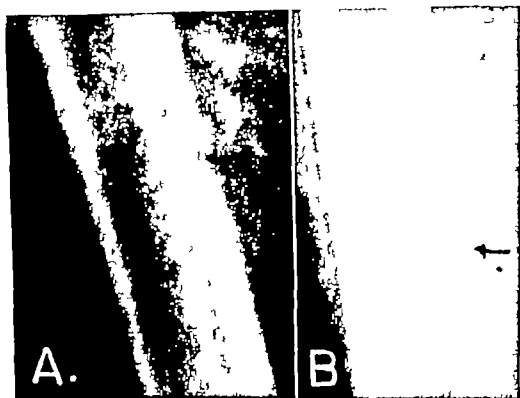


FIG 20 CASE 3, MILKMAN'S SYNDROME COMPLICATING NON TROPICAL SPRUE

X rays of femur (A) before vitamin D therapy (B) after one month of vitamin D (1 000 units daily) plus the benefit derived from the ultraviolet light of the springtime

case in contrast to case 2 there were no deficiencies of the fat-soluble vitamins other than vitamin D. Like case 2 this patient had free hydrochloric acid in her gastric contents early in her illness and only later showed achlorhydria. Anemia was a more prominent feature than in case 2.

She was treated with crude liver extract parenterally, large amounts of vitamin D (circa 50 000 units daily) a high calcium intake and iron.

She did very well on the whole. She was last seen on February 7 1945 at which time the haemoglobin was 12.8 gm /100 cc the serum calcium 9.8 mg /100 cc the serum phosphorus 3.0 mg /100 cc and the serum phosphatase 5.2 B U.

#### RENAL ACIDOSIS RESULTING FROM TUBULAR INSUFFICIENCY WITHOUT- GLOMERULAR INSUFFICIENCY

This section, in the authors' opinion, constitutes the most important part of this paper. Indeed, the chief purpose of the remainder of the paper is to make this section more understandable. Some conclusions will first be presented and then the evidence given.

Two important functions of the kidney tubules, to make ammonia and to excrete an acid urine, have to do with the conservation of base. Therefore in the presence of damaged kidney tubules one might expect a scarcity of base with

which to excrete acid. In this eventuality calcium, being a base, will be in demand and will appear in increased amounts in the urine. The serum calcium level will tend to fall. The sequence of events from here on will be the same as in vitamin D deficiency: the tendency to a low serum calcium level will lead to parathyroid hyperplasia, this will counteract the tendency to a low serum calcium level and will lead to hypophosphatemia, in the presence of a normal or slightly low serum calcium level and a low serum phosphorus level, calcium will not be deposited in osteoid and osteomalacia will result, the uncalcified new bone tissue will be less resistant to stresses and strains, this will lead to increased stimulation of the osteoblasts and to a high serum phosphatase level. It will be seen later that if there is a glomerular insufficiency along with the tubular insufficiency the above sequence of events is interrupted at one stage.

The disruption of homeostasis with renal acidosis resulting from tubular insufficiency is not confined to the above sequence. Potassium, being a base, also tends to be excreted in excess in the urine. The hyperkalemia may lead to hypokalemia and to the low potassium syndrome similar to that seen in family periodic paralysis. This aspect of renal acidosis had already been discussed in a paper from this hospital by Brown, Currens, and Marchand (41). Case 8 (see case abstract), who was first reported in this previous communication, had episodes characterized by pain in the extremities and inability to move arms and legs, these episodes were accompanied by a low serum potassium level and the characteristic changes in electrocardiogram (notably a lowering of the T waves) which one finds with hypokalemia. Case 9 (see case abstract) almost certainly developed the low potassium syndrome as a complication of a severe acidosis just before she died, unfortunately, no chemical or electrocardiographic evidence of hypokalemia was sought. The history of three days of paralysis in the arms and legs eight years prior to admission in case 6 (see case abstract) could very well have been due to this complication. Finally case 4, in an experimental study wherein she received for five days 130 m eq. of ammonium chloride daily, developed the prodromal symptoms of low serum potassium while the serum potassium fell and the potassium excretion in the urine mounted (see fig. 32).

Another possible ramification of the disordered electrolyte metabolism in tubular acidosis has to do with calcium absorption from the gastro-intestinal tract. Browne and Dineberg (42) have shown that gastric acidity is decreased in acidosis. This would tend to decrease the calcium absorption from the gastro-intestinal tract and would be another factor favoring the production of osteomalacia.

The present authors, contrary to the previously expressed opinion of Albright, Consolazio, Coombs, Sulkowitch, and Talbott (43), now believe that the nephrocalcinosis and the nephrolithiasis which frequently accompany this form of renal acidosis are complications of the disturbed homeostasis rather than causes. One strong piece of evidence in favor of this point of view lies in the fact that one meets essentially the same disturbance of homeostasis in cases without nephrocalcinosis or nephrolithiasis as in cases with these complications. Thus, the present analysis is based on eight cases: two of these (case 4 and case 5) had neither nephrolithiasis nor nephrocalcinosis, two cases (case 8 and case 9) had

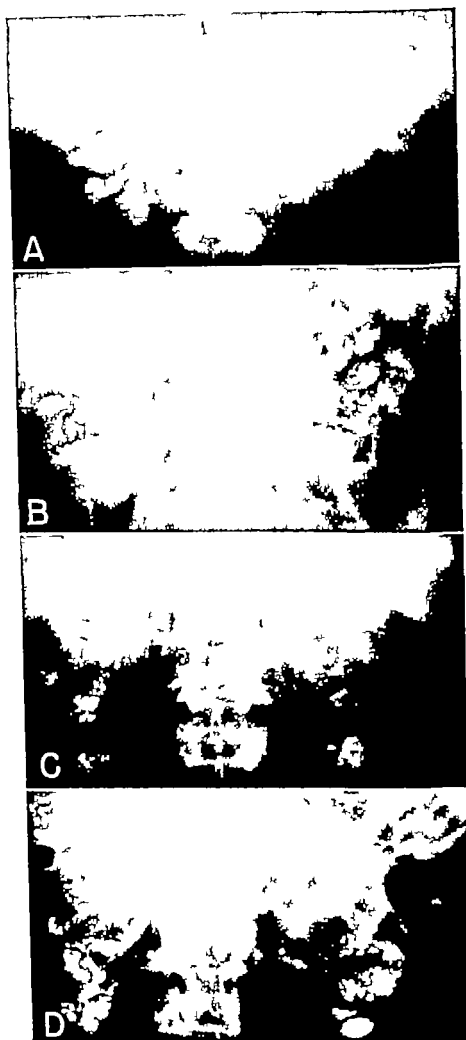


FIG 21 X RAYS ON FOUR CASES WITH RENAL ACIDOSIS AND NEPHROCALCINOSIS TO SHOW SIMILARITY

(A) Case of Butler Wilson and Farber (4), (B) case of Albright et al (43), (C) case 6 (D) case 7

nephrolithiasis without nephrocalcinosis, four cases (case reported by Butler, Wilson, and Faiber (44), case reported by Albright et al (43), case 6, and case 7) had both nephrolithiasis and nephrocalcinosis (see fig 21). A second argument in favor of the nephrolithiasis and nephrocalcinosis being secondary phenomena lies in the fact that these cases, when treated with alkali, do not form more

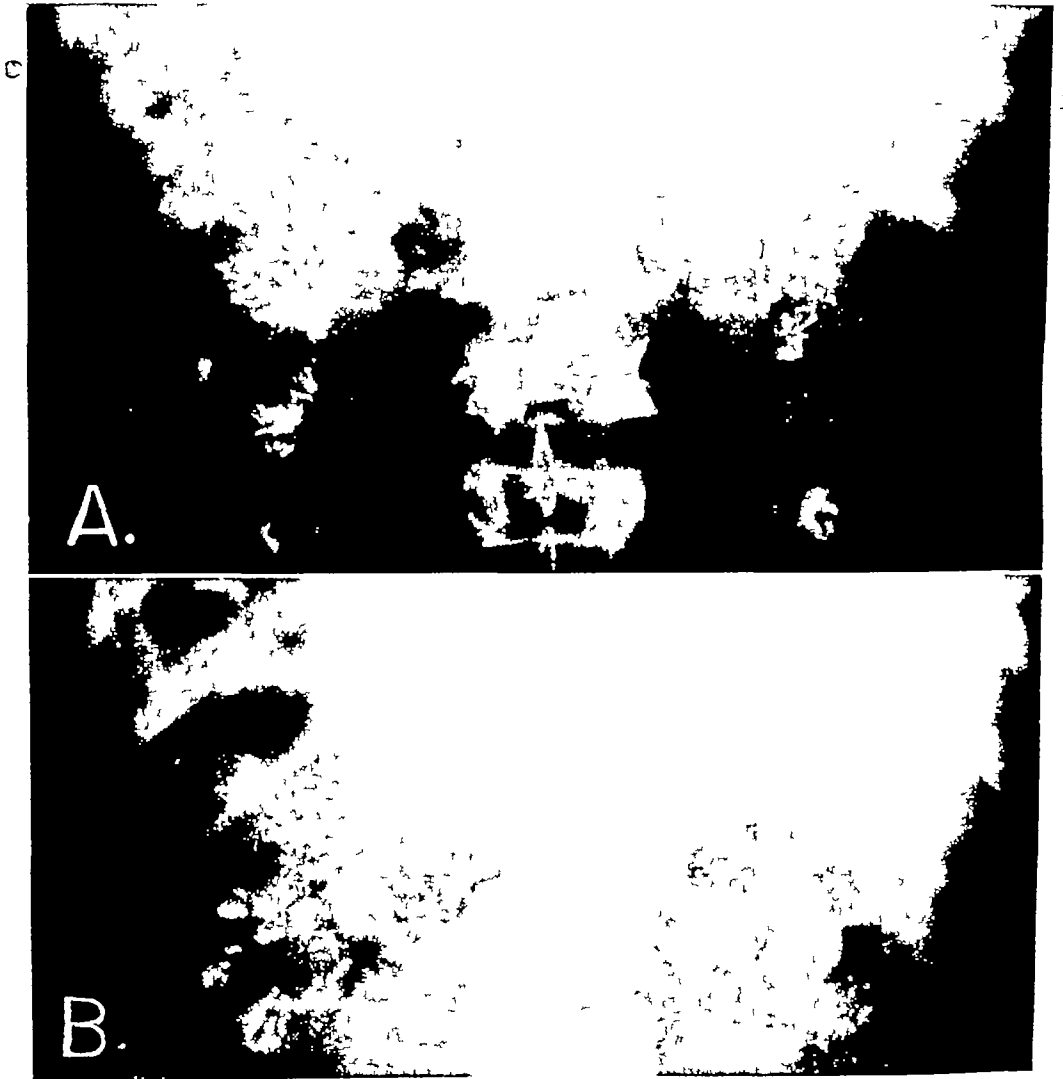


FIG 22 CASE 6 RENAL ACIDOSIS AND NEPHROCALCINOSIS  
(A) X-ray on 7-16-41, (B) X-ray on 10-13-44. Note marked diminution in number of stones

stones, indeed, since they continue to pass some of the stones, the number left in the kidneys often decreases. Since alkali therapy lowers the calcium excretion in the urine, this suggests that the hypercalcuria is the cause of the stones. The case reported by Albright et al (43), case 6, and case 7 all showed with alkali therapy a decrease in the number of stones (see fig 22). To be sure, case 7 showed an increase in the size of some of the stones after alkali therapy had been started (see fig 27). The reason for this was that infection had been introduced

during an ill advised attempt at retrograde dissolution. Cases 3 and 4 without kidney calcification did differ in one respect—the ability to concentrate the urine—from the group as a whole. Thus, the specific gravity of the urine reached 1.028 in case 3 and 1.018 in case 4, case 8 with nephrolithiasis but not nephrocalcinosis likewise had a urine specific gravity of 1.018, but the gravities of none of the other cases exceeded 1.012. This ability to concentrate the urine, despite marked tubular insufficiency, in cases 3 and 4 is a very interesting fact and may be an important clue. It suggests that the original tubular pathology does not involve the loops of Henle where most of the water is reabsorbed. This lack of hyposthenuria, by allowing urinary concentration, would favor precipitation of

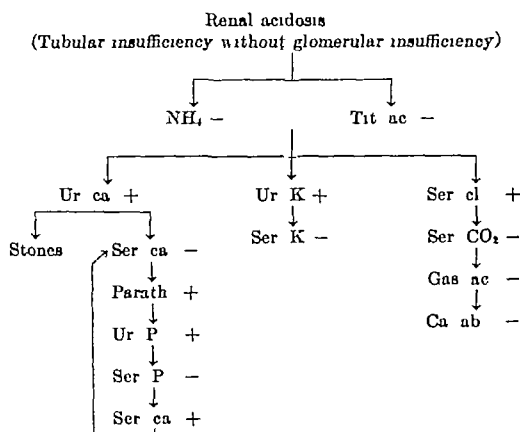


FIG. 23 SEQUENCE OF EVENTS IN DISORDERED HOMEOSTASIS RESULTING FROM RENAL ACIDOSIS OF THE TUBULAR INSUFFICIENCY WITHOUT GLOMERULAR INSUFFICIENCY TYPE

calcium in the tubules and the authors believe that the hyposthenuria present in those cases with nephrocalcinosis is at least one feature which is the result of the nephrocalcinosis.

In fig. 23 are depicted in diagrammatic form the relationships, one to the other, of the metabolic abnormalities in the syndrome under discussion.

It should be pointed out at this point that the condition under discussion and so-called "renal rickets" are two entirely different entities. The latter condition as pointed out by Albright, Drake and Sulkowitch (45) is not rickets at all but osteitis fibrosa generalisata. As regards the bone pathology in renal rickets, the emphasis is on increased bone destruction as opposed to lack of calcification or newly formed osteoid. To be sure, Follis and Jackson (46) have shown that even in renal rickets there is some delay in the calcification of newly formed osteoid, the present authors agree with this point of view. As a matter

of fact, the published photomicrographs of the case reported by Albright et al (45) show the osteoid seams to be slightly wider than normal. A fundamental difference in these two osteo-nephropathies lies in the kidney pathology itself. In the condition under discussion, one finds tubular dysfunction with relatively little glomerular insufficiency, in renal osteitis fibrosa generalisata (more commonly but less correctly termed "renal rickets") there is glomerular insufficiency as well as tubular insufficiency. The tubular insufficiency in renal rickets makes the first step in the derangement of homeostasis the same as in the condition under discussion,—namely there is a decreased ability to make ammonia and to excrete an acid urine, this leads to a demand for calcium for excretion in the urine as a base, this to a tendency to a low serum calcium level, this in turn to parathyroid hyperplasia, but here the sequence is interrupted! Because of the

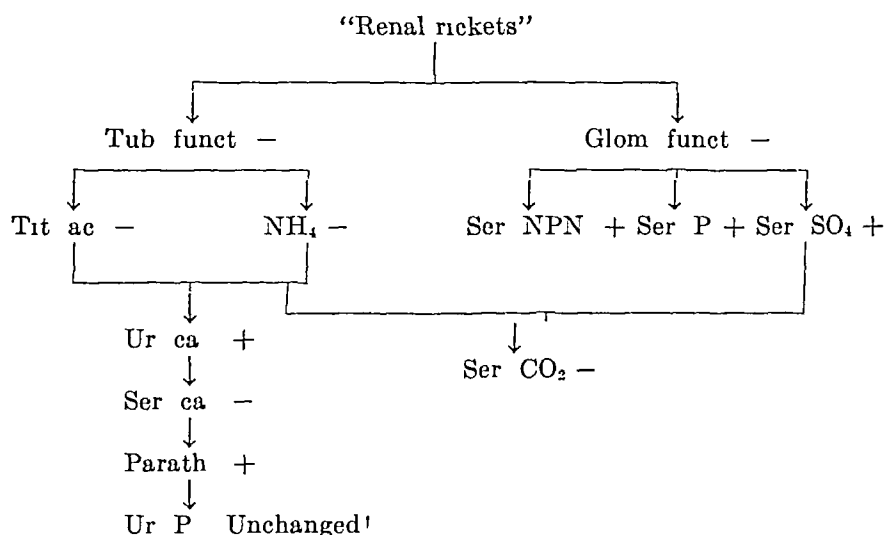


FIG 24 SEQUENCE OF EVENTS IN DISORDERED HOMEOSTASIS WITH "RENAL RICKETS"  
Compare with fig 23

glomerular disease, the increased parathyroid hormone does not produce a phosphorus diuresis and lower the elevated serum phosphorus level resulting from phosphorus retention, with a high serum phosphorus level there cannot be much delay in the deposition of calcium into the newly formed osteoid. Furthermore, in renal rickets there is usually marked retention of urea, creatinine, uric acid, sulphate, and potassium, and considerable impairment of phenolsulphonphthalein excretion. The acidosis in renal rickets, in short, is due not only to a shortage of base but to a retention of acid radicals, therefore it is not immediately corrected by the giving of base. In fig 24 are depicted in diagrammatic form the relationships, one to the other, of the metabolic abnormalities of renal osteitis fibrosa generalisata. This figure is to be contrasted with fig 23.

The etiology of the original kidney pathology in renal acidosis resulting from tubular-insufficiency-without-glomerular-insufficiency remains obscure. One first thinks of an ascending infection of the tubules from a pyelonephritis. The actual evidence for this in the eight well-advanced cases referred to in this paper



however, is slight. Only in case 6 and possibly in case 8 were urinary infections demonstrated. The case reported by Albright et al (43), case 4, case 5, case 7, and case 9 all had negative urinary cultures. There were no urinary cultures reported in the case of Butler et al (44). The autopsy findings in the kidneys in case 9 (see case history) are interesting but not too clear-cut. The fact that most of the glomeruli were uninvolved fits the clinical picture. It is also consistent that the most important changes were in the convoluted tubules. On the other hand, there was evidence of a low grade or a healed pyelonephritis. Thus, the nature of the primary pathological lesions remains obscure,—whether metabolic or enzymatic, whether infectious, whether degenerative.\*

The authors believe that renal acidosis of the sort under discussion leading to nephrocalcinosis and nephrolithiasis and at times to osteomalacia is relatively rare. Whereas they have limited the present discussion to eight well-defined cases, they believe that they have a few less complete cases in their Stone Clinic.<sup>†</sup> It is probably idiopathic hypercalcaemia to be discussed below and not the type of renal acidosis now being discussed which largely accounts for the findings of Flocks (47), this investigator noted that a large number of patients with renal calculi have hypercalcaemia coupled with disproportionate increase in urinary calcium excretion when vitamin D or an acid ash diet are given.

The response to treatment in these cases is most spectacular (see fig. 25, 26, and 27) and, since the treatment is based on the theoretical considerations just discussed, the validity of the theories is strengthened thereby. Inasmuch as the initial disturbance is a shortage of base, the first item of treatment is the administration of base. This is best given in the form of a salt of a mineral base with an organic acid, e.g. sodium citrate, sodium lactate, or calcium gluconate or, if hypokalaemia is a factor, a combination of sodium citrate and potassium citrate. The organic acid is burned after absorption, leaving the base free to help in the excretion of acid in the urine. An organic acid such as citric acid which will be largely burned after absorption can be given in addition to increase

\* Since the first paper was written there has appeared a very interesting case history by G. H. Daines, J. A. Barclay and W. T. Cooke (Nephrocalcinosis Associated with Hyperchloraemia and Low Plasma Bicarbonate. *Quart. J. Med. New Series* 14: 113, 1915). The patient, a 29-year-old woman, had bilateral renal stones, elevated serum chloride level, decreased plasma bicarbonate level, and a relatively fixed urinary specific gravity and pH. She responded to sodium citrate-citric acid therapy. She died after a severe reaction to sulfathiazole. Preliminary histopathological examination of the kidneys showed calcification in the pyramids and renal pelvis, but negligible amounts within the tubules and kidney tissues. The tubules themselves showed extensive vacuolation and an alteration in the type of epithelium. Occasional glomeruli were atrophied. There was no evidence of primary chronic vascular disease or glomerulonephritis. The authors felt that the findings were consistent with a non-inflammatory tubular defect. These authors also called attention to the autopsy findings in a case reported by J. D. Boyd and G. Stearns (*Am. J. Dis. Child.* 61: 1012, 1911) which showed only slight calcium deposits in the pyramids while the tubules were essentially normal, though the convoluted tubules were considerably dilated.

<sup>†</sup> The Stone Clinic was founded in 1935 as a joint enterprise of the Medical and Urological Services of the Massachusetts General Hospital to study the causes and prevention of renal calculi.

the gastrointestinal acidity and hence favor calcium absorption. The prescription advocated by Dr Alfred T Shohl and used by Albright et al (43) consisted of 140 grams of citric acid and 98 grams of sodium citrate dissolved in one liter of water, the patient takes 50 to 100 cc of this mixture daily depending on the amount needed to overcome the acidosis. Whereas such alkali therapy by itself will quickly restore the serum chloride level and  $\text{CO}_2$  content to normal, it will not cure the osteomalacia,—at least not in a short period of time. Since the cause of the osteomalacia in the first place is a shortage of base, the above state-

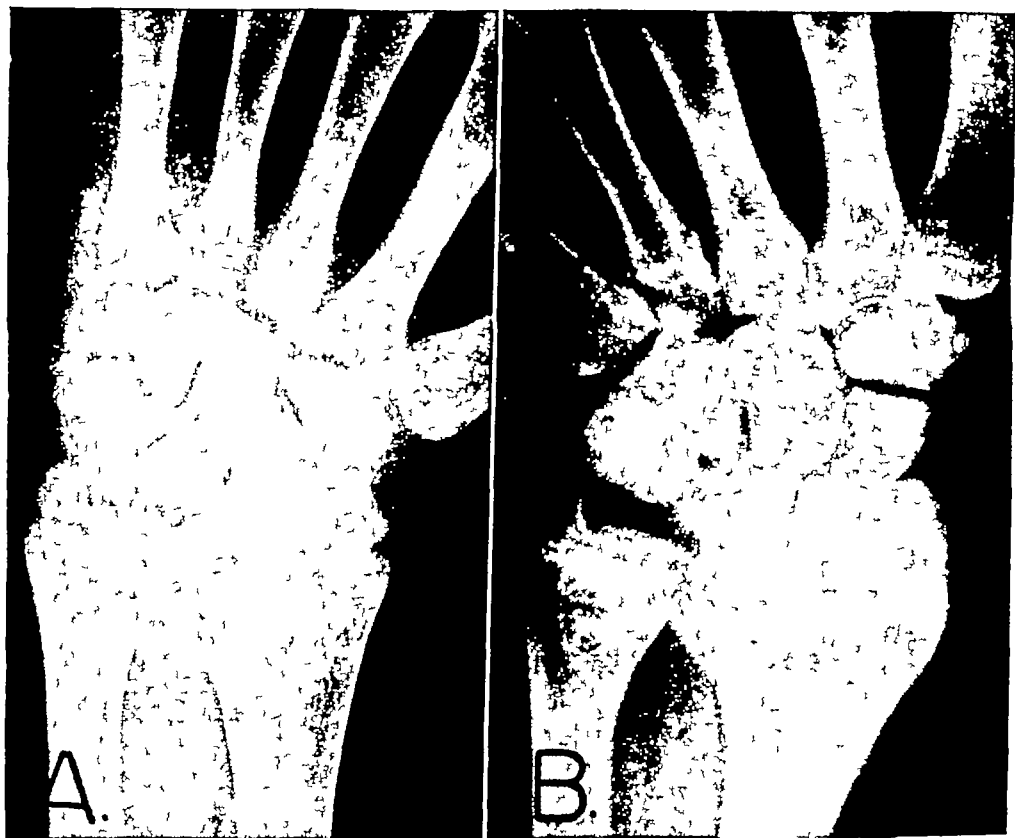


FIG 25 X-RAYS OF WRIST ON CASE 5 WITH RICKETS RESULTING FROM RENAL ACIDOSIS (A) BEFORE (1-10-39) AND (B) AFTER (2-24-39) HEALING OF RICKETS WITH MASSIVE DOSES OF VITAMIN D

ment at first seems contradictory. The explanation is probably one of simple arithmetic. The normal adult absorbs relatively little calcium (in round numbers let us say 100 mg daily) and, if in calcium equilibrium, excretes in the urine an amount equal to that which is absorbed<sup>8</sup>. If this individual now develops renal acidosis of the type under discussion, the calcium excretion in the urine may reach 300 to 500 mg daily, this will mean a loss to the body of 200 to 400 mg daily, if this goes on for months and years the skeleton will become depleted and the elevated calcium excretion in the urine will somewhat decrease. Now if

<sup>8</sup> In this arithmetic the amount of calcium absorbed and re-excreted in the bile is disregarded.

one overcomes the acidosis with alkali therapy, one can prevent further loss but the most one can hope to achieve in the way of a positive balance is 100 mg per day if the calcium excretion in the urine should fall to zero, but since the parathyroid hyperplasia keeps the serum calcium up to normal there will be some loss of calcium in the urine and the positive balance will be less than 100 mg per day. Therefore, the second step in therapy is the administration of an agent



FIG. 20. CASE 7 (A) X ray on 4-1-43 and (B) X ray on 7-7-43. Note that calluses of bilateral osteotomy performed on 6-25-42 were only incompletely calcified on 4-1-43 before therapy.

which will increase the calcium absorption from the gastro-intestinal tract, namely vitamin D. A combination of this with alkali therapy will bring about the desired end. Thus, vitamin D will cause calcium to be absorbed, alkali therapy will decrease its loss in the urine. If vitamin D is given alone a large part of the calcium which is absorbed will be re-excreted in the urine. If alkali therapy is given alone, very little calcium will be absorbed so that, in spite of little loss in the urine, the balance will still be only slightly positive. As a matter of fact, if one gives a very high calcium intake and massive doses of vitamin D,

so much calcium will be absorbed that, in spite of the large loss in the urine, the patient will be in positive calcium balance and the osteomalacia will be cured (see fig 25). Once the osteomalacia is cured, alkali therapy alone will prevent further bone disease.

The above treatment not only results in the alleviation of the bone disease but restores normal growth where the epiphyses are not yet united. The lack of skeletal growth in rickets has been attributed by some to a disorder other than that in the calcium metabolism. It is possible, however, to draw up a reasonable hypothesis to explain it on the basis of the disordered calcium metabolism.

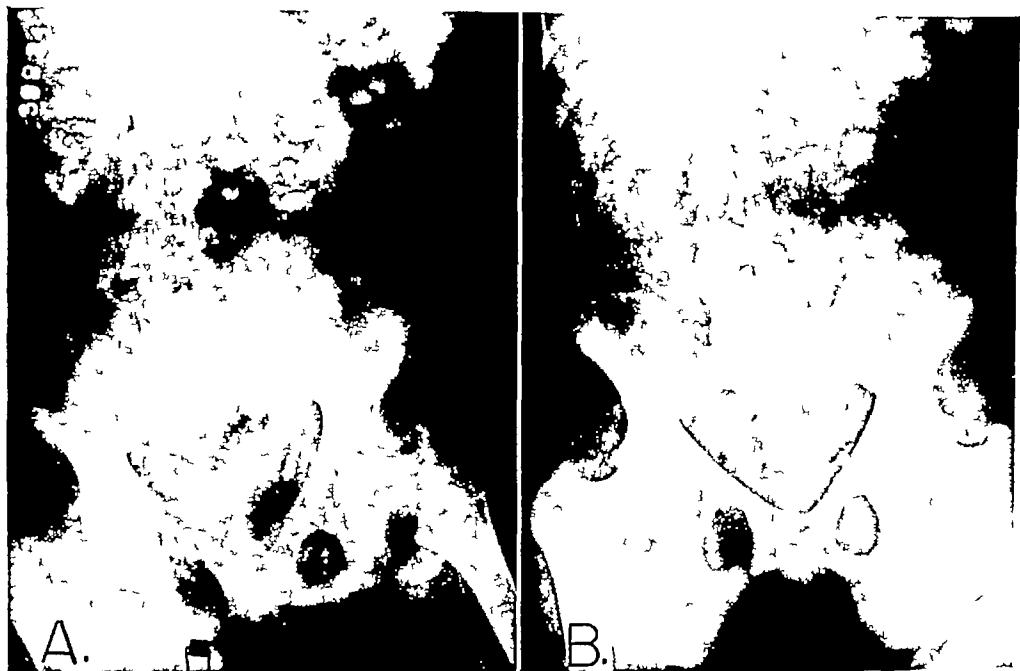


FIG 27 CASE 7, RENAL ACIDOSIS WITH OSTEOMALACIA AND NEPHROCALCINOSIS  
(A) X-ray on 3-30-43, (b) x-ray on 12-21-44. In "A" note increased radiability of bones, fractures of pubic rami, stones in lower end of right ureter, marked scoliosis and bilateral nephrocalcinosis. In "B" note normal density of bones, decreased degree of scoliosis, new collection of stones at lower end of right ureter, and decrease in number of kidney stones.

Thus, the sequence of events might be 1) relative unsaturation of body fluids with calcium phosphate, 2) failure of calcification of the zone of provisional calcification of cartilage, 3) failure of mature cartilage cells to die, 4) failure of blood vessels to break into holes left by dead cartilage cells, 5) continuation of proliferation of cartilage cells, 6) an increasing distance between proliferating cartilage cells and blood supply, and 7) failure of cartilage cells to proliferate due to lack of blood supply.

Before presenting the experimental data on which much of the above discussion is based, the case histories of the two experimental subjects will be presented.

#### Case 4 Diagnoses renal acidosis, Milkman's syndrome

M S P (M G H #237547), a 40-year-old white married laundress, first entered the Outpatient Department in February 1940, complaining of back pain for several years and of

pain and stiffness of the fingers of the left hand for one and one half years. She had lost 20 pounds in the preceding 2 years.

Physical examination revealed moderate atrophy of the left forearm, and severe atrophy of the left third, fourth, and fifth fingers. There was marked hyperesthesia of these parts.

Initial x ray examination showed severe decalcification of the left hand, most marked in the third, fourth, and fifth fingers. There was a pseudofracture of the left scapula (see fig 2F) the significance of which was not appreciated at that time. The spine was decalcified and showed scoliosis and kyphosis.

During the next year the patient was treated in numerous clinics in the Outpatient Department and was twice admitted to the hospital, once on the Orthopedic Service and once on the Neurological Service. However, the correct diagnosis was not made. She was considered to have psychoneurosis, she became progressively worse, the pains in her hand and back increased, pain in the pubic bones and later generalized bone pain developed. She lost an additional 20 pounds.

The patient again entered the hospital in March 1941. She was now a complete invalid due to her severe bone pains. Further x rays of the bones and a review of previous films led to the correct diagnosis of Milkman's syndrome.

These x rays revealed some decalcification of all bones. There were healed fractures of the distal ends of the shafts of the left radius and ulna and of two phalanges of the left hand. The left scapula still showed the pseudofracture previously described. No corresponding fracture was seen in the right scapula. There was an old fracture of the tenth rib on the right. In the pelvis were symmetrical pseudofractures radiating from the sacro iliac joints into the ilia and of the pubic bones running through the superior ramus. The skull was only moderately decalcified. The lamina dura was absent about most of the teeth.

Urine analysis showed moderate albuminuria, a specific gravity during a urine concentration test of 1.018, persistently a slight precipitate with Benedict's Solution, a urinary pH of 5.5, and many granular and hyaline casts in the sediment. Phenolsulphonphthalein excretion after intravenous administration was 8 per cent in 15 minutes, 7 per cent in  $\frac{1}{2}$  hour with a total of 28 per cent in 2 hours. The studies of the blood revealed 14 gm of haemoglobin, 4.35 million erythrocytes, 9,300 leucocytes, and a normal smear. Serum analyses showed calcium 9.5 mg/100 cc, phosphorus 1.9 mg/100 cc, phosphatase 7.5 B.U., non protein nitrogen 16 mg/100 cc, protein 6.9 gm/100 cc,  $\text{CO}_2$  combining power 16.9 m eq/liter, chloride 107.8 m eq/liter, total base 158 m eq/liter, and sodium 138.8 m eq/liter. The plasma pH was 7.27. A glucose tolerance test was normal. A tibial biopsy was performed; the bone was decalcified with Mueller's fluid. Dr. Granville A. Bennett did not consider the width of the osteoid seams greater than normal and considered the specimen normal.

On discharge on June 28, 1941, she was given vitamin  $\text{D}_2$  30,000 units daily and sufficient sodium citrate and calcium gluconate to control the acidosis and insure a high calcium intake. Within 2 months there was a dramatic improvement. By September 1941 the bone pain was decreased, she was able to walk, her appetite had increased, she was gaining weight. The fractures of the pelvis and right scapula were no longer visible in x rays taken during January 1942. Serum calcium, phosphorus, and phosphatase values returned to normal.

There was persistence, however, of the pain in the third, fourth, and fifth fingers of the left hand, this was considered to be a form of causalgia in some way connected with the healed fracture of the radius and a nerve crushing operation of the digital nerves of these fingers was performed by Dr. James G. White in June 1942, following which she was completely asymptomatic for six months. The pain then returned. In March 1943 her left ring finger was amputated, which gave complete and permanent relief from this mysterious pain.

The patient continued to be followed in the Outpatient Department. She continued to show a low  $\text{CO}_2$  content of the serum and a high serum chloride value when off medication, and normal values when on medication. The latter consisted of large amounts of vitamin

D (circa 50,000 units daily) and sodium citrate (circa 2 teaspoonsful of the crystals four times daily) In September 1944 she fell and broke her left arm, this healed without incident

On December 6, 1944 while asymptomatic, she consented to enter the metabolic ward for the studies discussed below in the text This opportunity was taken to check some of the laboratory findings The urine showed persistent albuminuria which was not orthostatic The urine sediment was essentially negative Four urine cultures showed "no growth" and there were no bacteria present in the urinary sediments (On two occasions in the Outpatient Department, cocci had been present in the urine, both in the sediment and on culture, this apparent infection had cleared up with sulfathiazole therapy in spite of the fact that she had taken the drug for only two days) Her urine reached a specific gravity of 1.018 during a urine concentration test Renal glycosuria to a very slight degree was probably present, but cystinuria was ruled out A phenolsulphonphthalein test showed 15 per cent excretion in 15 minutes, 5 per cent in 30 minutes with a total of 30 per cent in one hour Analyses of the serum showed calcium 10.1 mg/100 cc, phosphorus 3.5 mg/100 cc, alkaline phosphatase 5.1 B.U., protein 7.8 gm/100 cc, chloride 106.0 m eq/liter, CO<sub>2</sub> content 22.0 m eq/liter, sodium 137.0 m eq/liter, and potassium 4.0 m eq/liter The blood pressure was 120/80

#### Case 5 Diagnoses renal acidosis, late rickets

M. A. (M. G. H. #168199), a 17-year-old Canadian born female, first entered the Massachusetts General Hospital on January 7, 1939, complaining of deformities of the legs of 14 years duration

At 3 bowing of the legs was noticed, at 6 a diagnosis of rickets was made and cod liver oil and sunshine were prescribed, at 10 the patient was studied at the Shriner's Hospital for Crippled Children in Springfield, Massachusetts, where a diagnosis of renal rickets and dwarfism was made and corrective osteotomies were performed, at 13 she sustained a traumatic fracture of the right wrist which healed promptly but with deformity, at 15 her right femur was fractured as a result of trauma and healed in 6 weeks, but deformities of this leg increased, at 16 she developed a severe pain in the right upper leg and thereafter was unable to walk without crutches Urinalysis while at the Shriner's Hospital revealed albuminuria and the presence of occasional casts in the sediment, but normal renal function as judged by the phenolsulphonphthalein and urine concentration tests

The patient had had whooping cough and influenza at the age of 3, mumps at 6, and measles at 12 She had had frequent tonsillitis until a tonsillectomy at 12 Cod liver oil had been administered from early childhood until two years before entry, and she had had ample exposure to sunlight Catamenia had begun at the age of 15

The mother and father and six siblings were living and well

Physical examination except for short stature, multiple skeletal deformities characteristic of rickets, and a blood pressure of 110/80, was non-contributory

The urine analysis showed moderate albuminuria, rare leucocytes in the sediment, and a specific gravity of 1.028 during a urine concentration test Routine blood counts were normal The serum non-protein-nitrogen was 33 mg/100 cc, the serum protein 8.0 gm/100 cc, the serum calcium 11.2 and 9.7 mg/100 cc on two determinations, the serum phosphorus 2.2 mg/100 cc on each of two determinations, the serum phosphatase 16.3 B.U.

Roentgenographic examination of the skeleton (see fig. 25A and fig. 28) revealed marked generalized changes considered consistent with long standing rickets There was a pseudofracture at the upper end of the tibia (see fig. 28) Root formation of the teeth was retarded, the lamina dura was thin and in some places completely absent The distal epiphyseal lines of both radii and ulnae showed the characteristic changes of rickets (see fig. 25A) There were multiple old, incomplete, roughly symmetrical fractures of the femurs, tibiae, fibulae, and metatarsal bones

The chemical determinations and the x-ray findings made the diagnosis of rickets certain, it was felt at that time that the most likely cause of the rickets was a resistance to the usual doses of vitamin D She was, accordingly, given 120,000 units of vitamin D daily

and discharged to the Outpatient Department. An x ray of her right wrist taken 5 weeks later showed the rickets to be healed (see fig 25B). At this time the serum calcium was 12.5 mg/100 cc, the serum phosphorus 4.1 mg/100 cc, the serum phosphatase 14.2 B U.

Subsequently, her serum  $\text{CO}_2$  was found to be 17.8 m eq/liter (normal about 27 m eq). Because of this acidosis and the persistent albuminuria, it was felt that some abnormality of renal function might be the basis for her trouble. She was accordingly readmitted for further study on June 26, 1939. Vitamin D had been discontinued on April 22, 1939.

Urine analysis now revealed a pH of 5.5 to 6.0, moderate albuminuria, normal sediment, specific gravity of 1.028 during a urine concentration test, and no growth on culture. The



FIG 28 CASE 5 RENAL ACIDOSIS LATE RICKETS  
X rays of knees taken on 1-13-39. Note pseudofracture (arrow)

excretion of phenolsulphonphthalein after intravenous administration was 10 per cent in 15 minutes, 10 per cent in 30 minutes, 15 per cent in 60 minutes, making 35 per cent in all. The serum chloride was 111.0 m eq/liter, the serum  $\text{CO}_2$  content 18.1 m eq/liter, the serum calcium 10.8 mg/100 cc, the serum phosphorus 3.1 mg/100 cc, the serum phosphatase 13.4 B U. An intravenous pyelogram gave normal findings. The bones of the pelvis appeared more calcified than on the previous examination in January 1939.

The patient was given large doses of sodium citrate, 25-40 gm daily, for 7 days. On this regime her serum  $\text{CO}_2$  rose to 25 m eq/liter, her serum chloride fell to 109.0 m eq/liter, the urine pH rose to 7.5. The patient was again discharged to the Outpatient Department.

Subsequently (most recent visit November 4, 1944) she has remained in excellent health. Most of the time she has taken two teaspoonsful of sodium citrate crystals dissolved in water three times daily, at times she has taken moderate amounts of vitamin D. In May 1943 she was found to have a normal prothrombin time and normal contents of vitamin A and carotinoid in her blood. Further urine cultures and urine analyses made active pyelonephritis most unlikely.

# DIGRESSION ON COMPENSATORY MECHANISMS WHICH AID IN THE URINARY EXCRETION OF AN EXCESS OF ACID OR ALKALINE RADICALS

For the understanding of the experimental data to come later the present digression is almost essential. If the intake (diet, medications, etc.) contains an excess of inorganic acidic over basic radicals, i.e. an "acid ash" mixture, three chief mechanisms come into play to help excrete the excess acid and so to avoid an acidosis (Gamble, Blackfan, and Hamilton (48)).

The first and most important mechanism is the production by the kidney of ammonia. This mechanism requires some time—at least 5 days—to reach its maximum.

The second mechanism is the excretion of an acid urine. As the urinary pH decreases below the neutral point, more and more of the organic acid is excreted free without base and more of the phosphate is excreted in the form of primary phosphate as opposed to secondary phosphate. The saving thus attained is measured by the "titratable-acidity-of-the-urine" which is the amount of base necessary to bring the urine to a pH of 7.4. Since there is a minimum (4.7) to which the pH of the urine can decrease it is obvious that there is a limit to the titratable acidity depending on this minimum and the amounts of organic acid and phosphate in the urine.

The third mechanism is the dissolution of bone salts. Of these, the salts other than those of calcium are negligible. Shohl (49) states that 85 per cent of the calcium in the skeleton is in the form of tertiary calcium phosphate and 12 per cent in the form of calcium carbonate, this leaves 3 per cent unaccounted for. In the following calculations it will be assumed that this 3 per cent is combined with organic acids such as citric acid. At a pH of 7.4 the tertiary calcium phosphate would be excreted as a mixture of secondary phosphates (80 per cent) and primary phosphates (20 per cent), this would leave 40 per cent ( $\frac{1}{3} \times 80 + \frac{2}{3} \times 20 = 40$ ) of this calcium free for union with other acids. All the calcium of the calcium carbonate and of the calcium salts of other organic acids such as citric acid, provided the organic acid radicals are completely oxidized to  $\text{CO}_2$  and water, would be available for excretion with mineral acids in the urine. It will be seen, therefore, that 40 per cent of 85 per cent of the calcium dissolved from the bone and 100 per cent of the remaining 15 per cent (49 per cent in all) would be available for neutralizing mineral acids in the urine. To be sure, if the urine was acid, the calcium dissolved from the bone would have a greater net value but this added value is taken into account in the titratable acidity and so can be dismissed here.

There is a fourth mechanism,—the excretion of body fluids, notably extracellular fluids. In the presence of an acidosis, the body can excrete some of its fluid and hence make available part of the base of this fluid to neutralize acid. Since most of the base of this fluid is already off-set by mineral acids, the actual importance of this source of base is less than one would first think. Furthermore, one cannot keep on excreting body fluids so this mechanism must be considered as a temporary and limited one.

If the intake contains an excess of inorganic basic over acidic radicals, i.e. an "alkaline ash" mixture, the chief mechanism, as shown by Gamble (50), relative



to the neutralization of the excess of base in the urine is the large amount of carbonate so excreted at alkaline pH's. The concentration of carbonic acid in the urine rests, as does its plasma value, on the carbon dioxide tension in the alveolar air. Since the hydrogen ion concentration of the urine is determined by the ratio of free carbonic acid to bicarbonate, this fixed value for the numerator prescribes the individual values for bicarbonate over the range of urinary pH's (see fig 29). The interesting point brought out by fig 29 is the rapidity with which the bicarbonate in the urine increases as the pH rises above the neutral point. If one

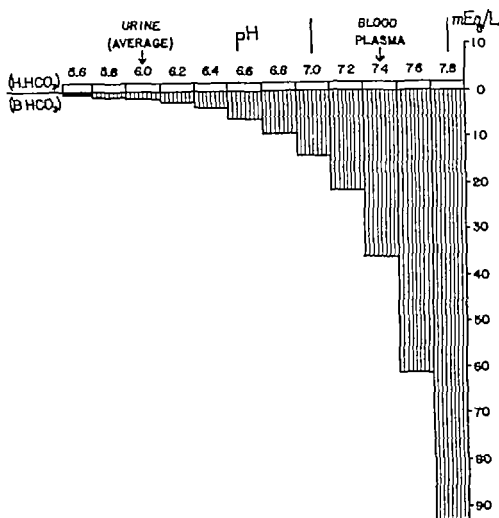


FIG 29 CARBONIC ACID AND BICARBONATE IN URINE

Diagram taken from Gamble (51) to illustrate the rapid increase in urinary bicarbonate as the urinary pH rises above the neutral point

The authors are indebted to Dr J C Gamble for permission to reproduce this figure

knows the pH of the urine and if one assumes a normal tension of carbon dioxide in the alveolar air, one can calculate the amount of bicarbonate in the urine by the Henderson Hasselbalch equation

$$\text{pH} = 6.1 + \log \text{BHCO}_3/\text{H}_2\text{CO}_3$$

In fig 36 (vide infra) some bicarbonate values derived from the above formula are compared with the actual bicarbonate found, all things considered, the agreement is surprisingly good

From the above discussion it is seen that the ammonia, plus the titratable acidity, plus 49 per cent of the calcium mobilized from the skeleton serves as spacers of base, while the bicarbonate in the urine serves to remove any surplus of base which may have been ingested or which the base spacers may have pro-

\* By base is meant fixed base — i.e.  $\text{N}_2$ , K, Ca, and Mg

vided, urinary bicarbonate, therefore, is a negative sparer as it were. This gives us the following quantitative expression for the sum-of-the-base-sparing-mechanisms (S B S)

$$SBS = NH_4 + \text{tit ac} + 49/100 \text{ Ca} - \text{BHCO}_3$$

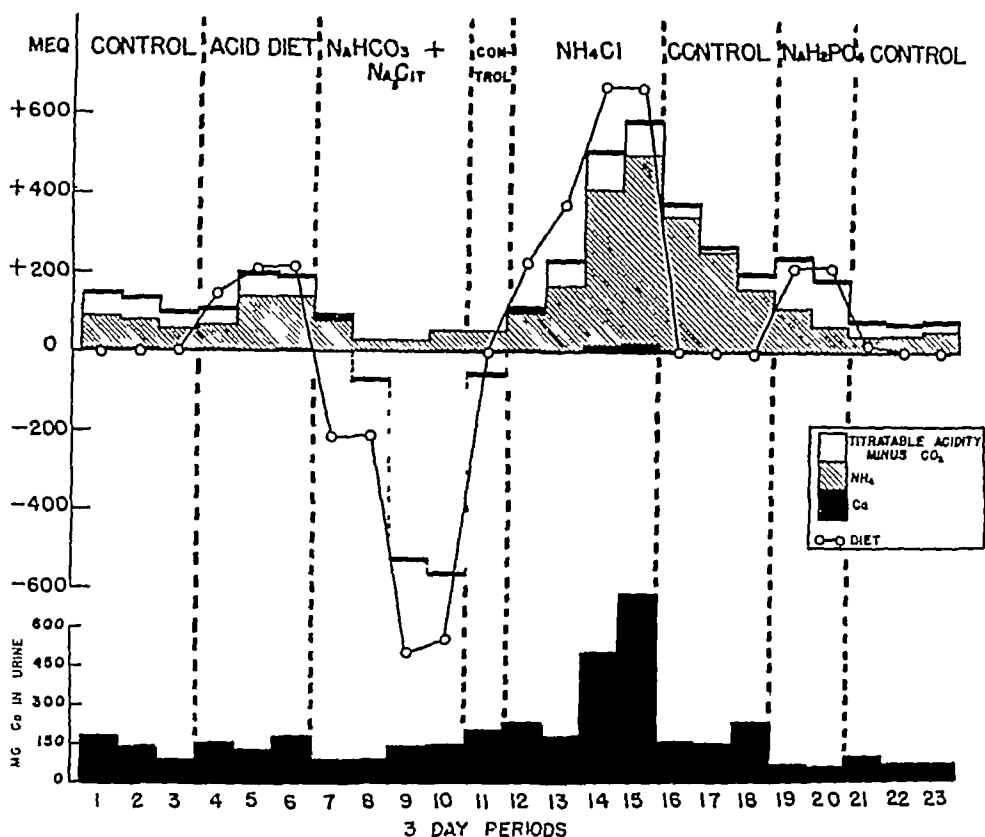


FIG 30 COMPARISON OF THE ACID VALUES OF THE DIET WITH THE S B S ("SUM OF BASE SPARERS") UNDER NEUTRAL, ACID, AND ALKALINE REGIMES

The base sparingers—calcium mobilized from skeleton, ammonia, and "titratable-acidity-minus- $\text{CO}_2$ "—are charted one on top of the other in the order given, where the titratable-acidity-minus- $\text{CO}_2$  is a negative value it is subtracted from the sum of the other two (see periods 7 through 12). The data are charted as 3-day values. In calculating the calcium components of the S B S, 49 per cent of the urinary calcium was taken although not all the urinary calcium was necessarily derived from the skeleton, it should be noted that, in spite of this, the values so charted were insignificant and became detectable in the diagram only during periods 14 and 15. The calcium is charted separately with a larger scale at the bottom to show the marked increase in excretion with ammonium chloride, and the failure of the excretion to increase with sodium acid phosphate. For further discussion of diagram, see text. The data for this diagram are taken from Farquharson, Salter, and Aub (53) and are presented here with the permission of the Journal of Clinical Investigation. The authors are indebted to Dr. Harry Klinefelter for the preparation of this diagram.

where Ca represents that aliquot of calcium excretion which is derived from the skeleton, namely the negative calcium balance. However, the determination of the titratable acidity and that of the bicarbonate in the urine offer some difficulty due to the ease with which carbonic acid diffuses off. This difficulty can be circumvented by omitting both of these determinations and measuring in their place the "titratable-acidity-minus- $\text{CO}_2$ " (Albright, Bauer, Ropes, and Aub (52)). This value is obtained by adding a known amount of hydrochloric acid to the

urine, aerating until all the  $\text{CO}_2$  is driven off, and then titrating back to a pH of 7.4. The answer is obtained by subtracting the amount of acid added from the amount of alkali used in the titration.

In fig 30 some very interesting and pertinent data from a paper by Farquarson, Salter, and Aub (53) are presented in diagrammatic form<sup>10</sup> The data pertain to a man of 37 who was convalescing from lead poisoning and show the effect of various acid and alkaline regimes on the S.B.S. The first point brought out in fig 30 is the fairly good parallelism between the S.B.S. and the acidity or alkalinity of the ash of the intake (diet plus medication), it should be noted that the S.B.S. is not zero on a neutral regime, this is understandable because a neutral ash diet means equivalence of fixed base and the sum of the radicals of the inorganic acids, —  $\text{Cl}$ ,  $\text{HPO}_4$ , and  $\text{SO}_4$ , there is, however, a fourth component of the total acid excretion, a group of organic acids which must be covered by S.B.S. Of interest, secondly, in fig 30 is the insignificance of the calcium mobilized from the skeleton as a factor in the S.B.S. despite the marked increase in the excretion during the administration of  $\text{NH}_4\text{Cl}$  (see periods 14 and 15). The third point to be noted is the tendency for the titratable-acidity-minus- $\text{CO}_2$  to reach a limit on the positive side as discussed above (compare periods 14 and 15 with period 13). Other points of interest in fig 30 are the delay in the ammonia excretion in reaching a maximum, the effect of an increase in phosphate intake on the degree of positivity of the titratable acidity-minus- $\text{CO}_2$  (see periods 19 and 20), and, since in a sufficiently acid urine sodium acid phosphate requires no added base, the failure of this salt as compared with ammonium chloride to pull out ammonia and calcium. This last point is all important in the clinical problem of acidifying the urine to prevent the formation of calcium phosphate calculi, but this is aside from the present discussion. Finally, it should be noted in fig 30 that the S.B.S. did not quite compensate for the increased acidity of the intake when ammonium chloride was added in periods 12 through 15. As had to be the case, this did result in a blood acidosis with a plasma  $\text{CO}_2$  content of 14.5 m.eq./liter in period 15.

#### METABOLIC DATA ON CASES OF RENAL ACIDOSIS RESULTING FROM TUBULAR-INSUFFICIENCY-WITHOUT-GLOMERULAR-INSUFFICIENCY

*Experiment 1—Effect of neutral ash, acid ash, and alkaline ash intakes on S.B.S., calcium metabolism, and potassium metabolism of patient with renal acidosis of the specific type*

In fig 31 and table 1 are presented some data on case 4 obtained during a 33 day study at a time (Dec 1944) when the osteomalacia had been completely cured by previous therapy. She was studied for 12 days on a neutral ash diet, for 5 days on an acid ash regime (neutral ash diet plus 130 m.eq. of ammonium chloride by mouth per 24-hours), for 7 days back on the neutral ash diet, and finally for 9 days on a alkaline ash regime (neutral ash diet plus 350 m.eq. of sodium lactate per 24-hour by mouth). For a considerable period before the onset of the investigation and throughout the entire investigation, the patient received

<sup>10</sup> The same data were charted in a somewhat different manner by Salter, Farquarson, and Tibbetts (54).

TABLE 1

*Metabolic data for experiment 1*  
Case 4 Renal acidosis (M St P 237547)

DAY	NITROGEN (GM /24 HR )				PHOSPHORUS (MG /24 HR )				CALCIUM (MG /24 HR )				POTASSIUM (M.EQ / 24 HR )				DATA FOR S.B.S (M.EQ / 24 HR )				S.B.S *	ACIDITY OF INTAKE	SERUM					
	Urine		Feces		Urine	Feces	Int	Bal	Urine	Feces	Int	Bal	Urine	Feces	Int	Bal	49% of negative Ca balance	NH <sub>4</sub>	Tit ac-CO <sub>2</sub>	CO <sub>2</sub>			Cl	pH	K	Ca	P	
	Int	Bal.	Int	Bal.																								
1	10 197	0 840	9 15	-1 89	788	106	633	-261	204	39	76	-227	63 11	5 93	58 2	-10 8	5 56	34 3	12 67	52 53	0	22 3	106					
2	10 197	0 840	9 15	-1 89	788	106	633	-261	204	39	76	-227	63 11	5 93	58 2	-10 8	5 56	36 0	8 10	49 66	0							
3	10 197	0 840	9 15	-1 89	788	106	633	-261	204	39	76	-227	63 11	5 93	58 2	-10 8	5 56	31 6	8 84	45 23	0							
4	8 830	0 840	9 15	-0 52	657	106	633	-130	232	39	76	-105	48 05	5 93	58 2	+4 2	4 78	31 4	6 50	42 68	0							
5	8 830	0 840	9 15	-0 52	657	106	633	-130	232	39	76	-105	48 05	5 93	58 2	+4 2	4 78	33 5	5 44	43 72	0							
6	8 830	0 840	9 15	-0 52	657	106	633	-130	232	39	76	-105	48 05	5 93	58 2	+4 2	4 78	33 5	5 44	43 72	0							
7	8 823	1 001	9 15	-0 67	662	117	633	-146	238	40	76	-202	54 36	6 30	58 2	-2 5	4 95	35 4	3 71	44 06	0							
8	8 823	1 001	9 15	-0 67	662	117	633	-146	238	40	76	-202	54 36	6 30	58 2	-2 5	4 95	34 5	1 49	40 94	0							
9	8 823	1 001	9 15	-0 67	662	117	633	-146	238	40	76	-202	54 36	6 30	58 2	-2 5	4 95	32 2	2 05	39 87	0							
10	8 832	1 001	9 15	-0 48	637	117	633	-121	236	40	76	-200	50 32	6 30	58 2	+1 6	4 90	32 9	0 82	37 62	0							
11	8 832	1 001	9 15	-0 48	637	117	633	-121	236	40	76	-200	50 32	6 30	58 2	+1 6	4 90	32 5	2 72	40 12	0							
12	8 832	1 001	9 15	-0 48	637	117	633	-121	236	40	76	-200	50 32	6 30	58 2	+1 6	4 90	32 5	16 96	63 44	130							
13	9 414	0 885	11 01	+1 09	723	73	633	-163	344	29	76	-297	69 69	5 28	58 2	-16 8	7 28	39 2	35 53	88 51	130							
14	9 414	0 885	11 01	+1 09	723	73	633	-163	344	29	76	-297	69 69	5 28	58 2	-16 8	7 28	45 7			130							
15	9 414	0 885	11 01	+1 09	723	73	633	-163	344	29	76	-297	69 69	5 28	58 2	-16 8	7 28	68 9	42 34	122 63	130							
16	10 422	0 685	11 01	-0 10	745	73	633	-185	471	29	76	-424	90 77	5 28	58 2	-37 9	10 39	58 9	33 90	99 71	21							
17	10 422	0 685	11 01	-0 10	745	73	633	-185	471	29	76	-424	90 77	5 28	58 2	-37 9	10 39	58 9	33 90	99 71	21							
18	8 462	0 628	4 91	-4 00	540	90	351	-308	309	26	58	-282	42 54	4 80	34 9	-14 0	6 91	58 9	42 34	122 63	130							
19	8 462	0 628	4 91	-4 60	540	90	351	-308	309	26	58	-282	42 54	4 80	34 9	-14 0	6 91	53 4	25 40	85 71	0							
20	8 462	0 628	4 91	-4 60	540	90	351	-308	309	26	58	-282	42 54	4 80	34 9	-14 0	6 91	56 2	23 65	88 76	0							
21	8 462	0 628	4 91	-4 60	540	90	351	-308	309	26	58	-282	42 54	4 80	34 9	-14 0	6 91	55 2	17 50	79 61	0							
22	9 133	0 628	8 72	-1 04	511	90	604	+3	250	26	73	-203	43 43	4 80	34 9	+9 5	4 97	39 7	7 74	52 41	0							
23	9 133	0 628	8 72	-1 04	511	90	604	+3	250	26	73	-203	43 43	4 80	34 9	+9 5	4 97				0							
24	9 133	0 628	8 72	-1 04	511	90	604	+3	250	26	73	-203	43 43	4 80	34 9	+9 5	4 97				0							



**TABLE 1**  
*Metabolic data for experiment 1*  
Case 4 Renal acidosis (M St P 237547)

DAY	NITROGEN (CM /24 HR.)				PHOSPHORUS (MG /24 HR.)				CALCIUM (MG /24 HR.)				POTASSIUM (MEQ /24 HR.)				DATA FOR S.B.S. (MEQ /24 HR.)				S.B.S.*	ACIDITY OF INTAKE	SERUM																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
	Urine	Feces	Int	Bal.	Urine	Feces	Int	Bal.	Urine	Feces	Int	Bal.	49% of nega-tive Ca balance	NH <sub>4</sub>	Tit ac-CO <sub>2</sub>	CO <sub>2</sub>	Cl	pH	K	Ca			P																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
1	10 197	0 840	9 15	-1 89	788	106	633	-261	204	39	76	-227	63 11	5 93	58 2	-10 8	5 56	34 3	12 67	52 53	0	22 3	106																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						



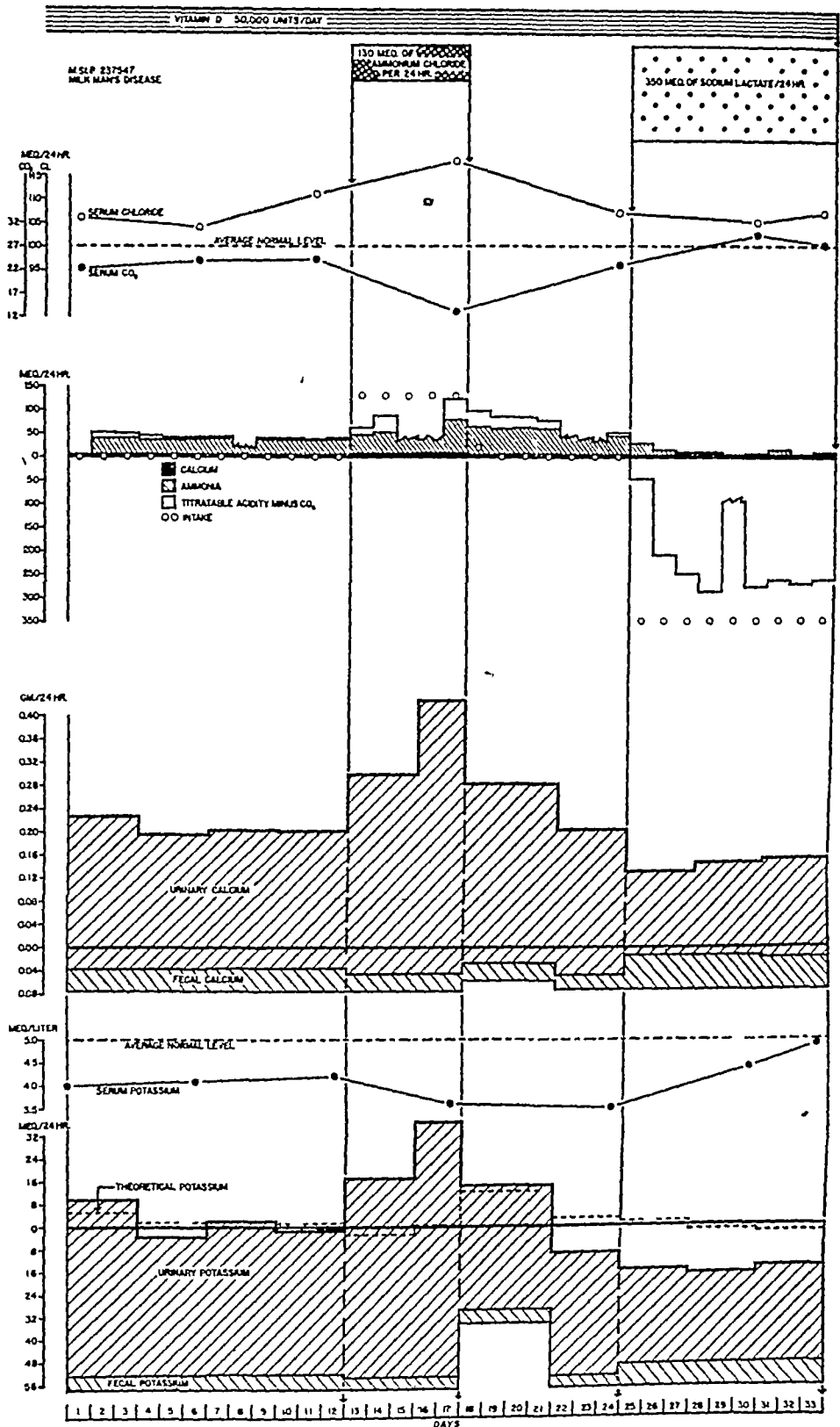


FIG 31 EXPERIMENT 1, CASE 4, RENAL ACIDOSIS AND CURED MILKMAN'S SYNDROME  
A comparison of the effect of a neutral ash regime with an acid ash regime and an alkaline ash regime For discussion see text



50,000 units of vitamin D daily, this insured an adequate calcium absorption and precluded any changes in calcium metabolism resulting from fluctuations in the ultra-violet light in the atmosphere. On day 17, the last day of the ammonium chloride administration, the patient developed pain in her arms which is often the first symptom of the low potassium syndrome and for four days thereafter was unable to eat all her diet, this explains the decreased intakes during days 18 through 21.

*Serum chloride and serum  $\text{CO}_2$  content* At the top of fig 31 it will be seen that during the 12 days on the neutral ash regime the serum chloride and serum  $\text{CO}_2$  content were within normal limits, that with the administration of ammonium chloride the serum chloride rose to a high level (112 m.eq./liter) and the  $\text{CO}_2$  content fell to a low level (13.0 m.eq./liter), that during the control days back on the neutral ash regime these values returned to normal, and that finally, with the administration of sodium lactate, there was a further slight rise in  $\text{CO}_2$  content.

*Comparison of S.B.S. with acidity value of ash intake* Note in fig 31, as in fig 30, that the calcium component of the S.B.S. is negligible throughout, that, as in fig 30, the S.B.S. has an appreciably positive value to offset the organic acids during the neutral ash regime (see days 1 through 12), that with the administration of ammonium chloride the S.B.S. does not rise as much as the acidity value of the intake which makes a blood acidosis a necessary sequel, that with the omission of ammonium chloride (days 18 through 21) the S.B.S. continues high until the acidosis is dispelled (day 24), and, finally, that with the administration of sodium lactate the S.B.S. becomes a negative value but not quite so negative as the acidity of the regime, presumably because of the continued presence of organic acid in the urine. Indeed, the discrepancy between the acidity of the regime and the S.B.S. is greater with the alkaline regime than during the neutral regime, this suggests an increase in organic acid excretion during the alkaline regime which is what one would expect. The important point for the argument at hand, however, is the fact that the S.B.S., while definitely rising, does not rise sufficiently to compensate for the 130 m.eq. increase in acidity during the administration of ammonium chloride, this speaks for an impaired tubular function as hypothesized above. In fig 32 (vide infra) these data will be compared with those from a normal individual who received the same amount of ammonium chloride. The "normal individual" in fig 30 received 224 m.eq. of ammonium chloride daily instead of 130 m.eq. so the data on him cannot be used in comparison.

*Calcium metabolism* It will be noted in fig 31 that the calcium metabolism behaves in accordance with the hypothesis outlined above. Thus, during the neutral ash regime (days 1 through 12) there is a large amount of calcium in the urine and a large negative calcium balance, with the ammonium chloride administration there is a sharp rise in the urinary calcium excretion, with the omission of ammonium chloride there is a return to the initial level of calcium excretion, and, finally, with the administration of sodium lactate there is a definite fall in the urinary calcium excretion. As in fig 30, the parallelism between the ammonia and the calcium excretions in the urine should be noted.

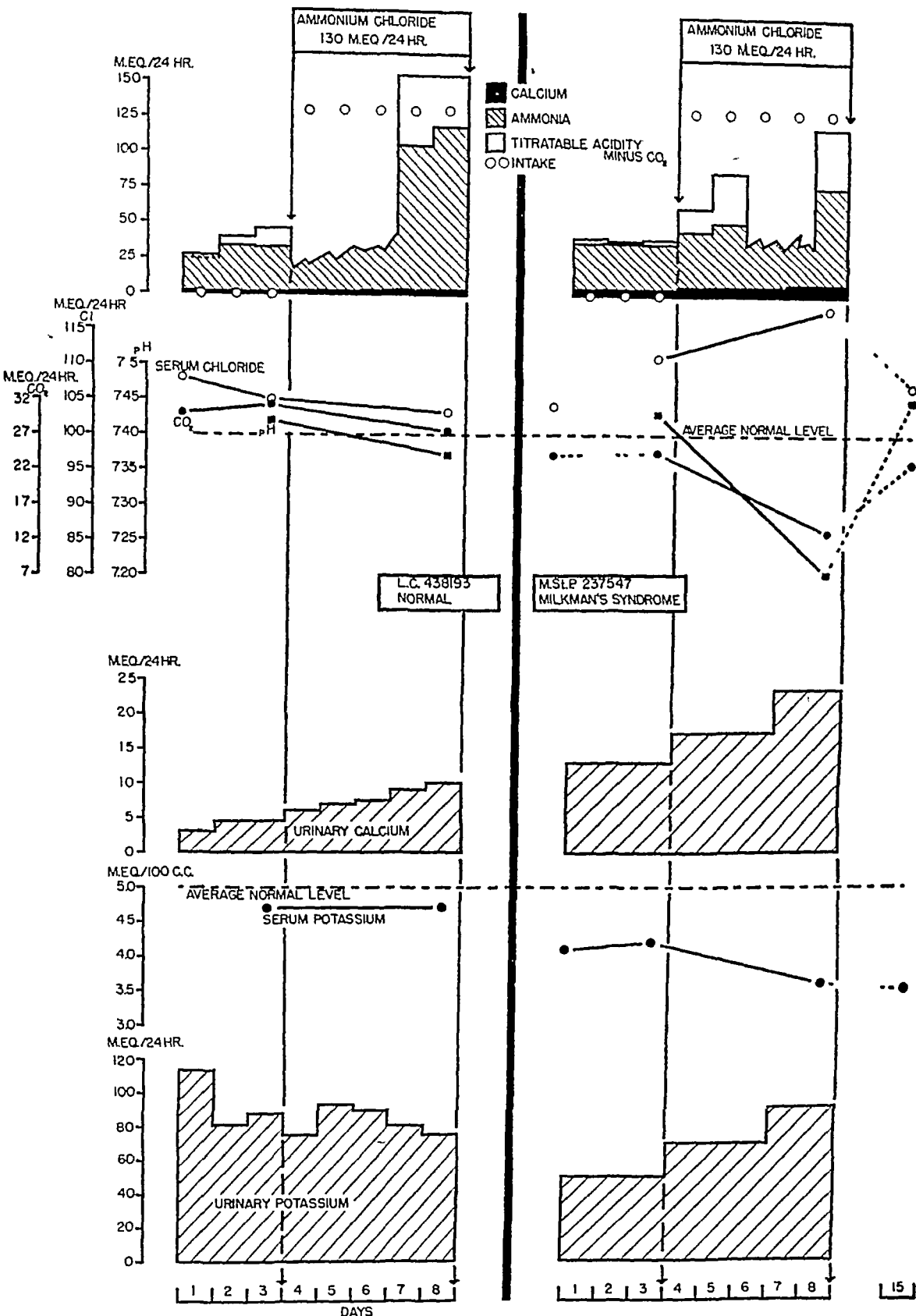


FIG 32 EXPERIMENT 2, CASE 4, COMPARISON OF THE EFFECT OF 130 M EQ OF AMMONIUM CHLORIDE ON A NORMAL INDIVIDUAL AND A PATIENT WITH RENAL ACIDOSIS  
For discussion see text

*Potassium metabolism* In the potassium metabolism data at the bottom of fig 31 note that the urinary excretion parallels the urinary calcium excretion very closely Thus, during the neutral regime there is potassium equilibrium, with the administration of ammonium chloride there is a sharp increase in the urinary potassium excretion and a fall in the serum potassium level, with cessation of the ammonium chloride administration there is a lowering in the urinary potassium excretion, finally, with the administration of sodium lactate there is a strongly positive potassium balance and a rise in the serum potassium level The theoretical potassium balance, by which is meant the balance which one would calculate on the assumption that the potassium balance is dependent on the amount of protoplasm ( $1 \text{ gm N} = 2.7 \text{ m.eq K}$ ) formed or destroyed, is most instructive (see dotted line) It will be noted that, with the administration of ammonium chloride, the actual potassium balance becomes strongly negative while the theoretical balance remains unchanged This is an indication that the potassium loss during acidosis is not due to destruction of protoplasm. It will be further noted that with the administration of sodium lactate there is a strongly positive actual potassium balance while the theoretical potassium balance remains essentially zero

*Experiment 2—Effect of 130 m eq of ammonium chloride daily on patient with renal acidosis compared with effect on a normal individual*

The thesis under investigation holds that the individual with this special type of renal acidosis cannot compensate for an excess of acid in the intake as effectively as a normal individual It was therefore important to study an individual with renal acidosis and a normal individual under conditions as nearly the same as possible This was done and the data are shown in fig 32 and table 2 The data on the right side of fig 32 are the same data as shown for days 10 through 17 in fig 31 The data on the left side of fig 32 represent the corresponding data for the normal individual Both individuals ate the same neutral ash diet except that the normal individual, having a somewhat greater energy output, received 20 per cent extra of each component of the diet, both individuals received 130 m eq ammonium chloride for five days Charted in fig 32 are three control days on the diet alone followed by five days of ammonium chloride administration The most important feature of the experiment concerns the changes in ammonia and titratable-acidity-minus  $\text{CO}_2$  as a result of the administration of ammonium chloride, whereas both individuals had a marked increase in both of these factors, in the normal individual the combined increase ( $118.0 \text{ m eq}$  on 5th day of ammonium chloride administration) almost offset the increase in acidity ( $130 \text{ m eq}$ ) whereas in the patient with renal acidosis the combined increase ( $77.0 \text{ m eq}$ ) on the 5th day of ammonium chloride administration fell far short of this Consequently, the serum chloride,  $\text{CO}_2$  content, and pH in the normal individual showed no significant changes, in the patient with renal acidosis, on the other hand, there was a marked rise in the serum chloride, and a marked fall in the serum  $\text{CO}_2$  content and in the serum pH The calcium excretion in the normal individual rose slightly, in the patient with renal acidosis it rose markedly

Finally, there was no change in urinary potassium excretion in the normal individual, whereas there was a marked increase in the patient with renal acidosis accompanied by a fall in the serum potassium level

*Experiment 3—Studies of calcium, phosphorus, and nitrogen balances on patient with renal acidosis to show effect of alkali therapy alone, alkali therapy with vitamin D, and vitamin D alone*

As discussed above under section on treatment, the best results are obtained with both alkali and vitamin D therapy It was stated that alkali therapy alone

TABLE 2  
Metabolic data for experiment 3

DAY	URINE				49 PER CENT OF NEGA- TIVE Ca BALANCE	S.B S *	ACIDITY OF INTAKE	SERUM			
	K	Ca	NH <sub>4</sub>	Tit Ac. CO <sub>2</sub>				CO <sub>2</sub>	Cl	pH	K
Normal control (L C 438193)											
	<i>m eq</i>	<i>m eq</i>	<i>m eq</i>	<i>m eq</i>	<i>m eq</i>	<i>m eq</i>	<i>m eq</i>	<i>m eq</i> /l	<i>m eq</i> /l		<i>m eq</i> /l
1	113 76	3 3	25 3	-1 73	0	23 57	0	29 8	108 0		
2	80 98	4 5	32 0	6 11	0	38 11	0				
3	87 75	4 5	31 8	12 54	0	44 34	0				
4	75 11	6 1			0 98		130	31 3	105 0	7 42	4 7
5	92 56	7 1			1 47		130				
6	89 42	7 4	105 8	44 86	1 62	152 28	130				
7	80 22	9 0	111 8	39 82	2 40	154 02	130				
8	75 23	9 8	118 4	44 46	2 79	165 65	130	27 4	103 0	7 37	4 7
Case 4 Renal acidosis (M St P 237547)											
1	50 32	11 8	32 2	2 95	4 9	40 05	0	23 9	104 0		4 1
2	50 32	11 8	32 9	0 82	4 9	38 62	0				
3	50 32	11 8	32 5	2 72	4 9	40 12	0				
4	69 69	17 2	39 2	16 96	14 9	71 06	130	24 4	111 0	7 43	4 2
5	69 69	17 2	45 7	35 53	14 9	96 13	130				
6	69 69	17 2			14 9		130				
7	90 77	23 6			21 2		130				
8	90 77	23 6	69 9	42 34	21 2	133 44	130	13 0	118 0	7 20	3 6
15								23 0	107 0	7 45	3 5

\* Sum-of-the-base-sparers

diminishes the urinary calcium excretion but that this does not make enough difference in the calcium balance to produce dramatic changes, that vitamin D alone causes a marked increase in calcium absorption but that a large part of the calcium is reexcreted in the urine to offset the acidosis, that, however, with the above therapeutic agents together calcium is absorbed in large amounts and is not reexcreted in the urine The data shown in fig 33 and table 3, obtained on patient 5 at a time when her osteomalacia had been cured by previous therapy, support these contentions The data are self-explanatory At the top of fig. 33 it will be noted that the nitrogen metabolism was not significantly affected

by either of the therapeutic agents. The serum chloride was high and the  $\text{CO}_2$  content was low when the patient was not receiving the alkali, both of these values were normal when she was. The phosphorus metabolism (see fig 33) by and large followed the calcium metabolism and requires no further discussion.

*Calcium metabolism.* Unfortunately, a slightly alkaline ash diet (2 m eq) was employed for the entire 42 3-day periods. This probably accounts for the

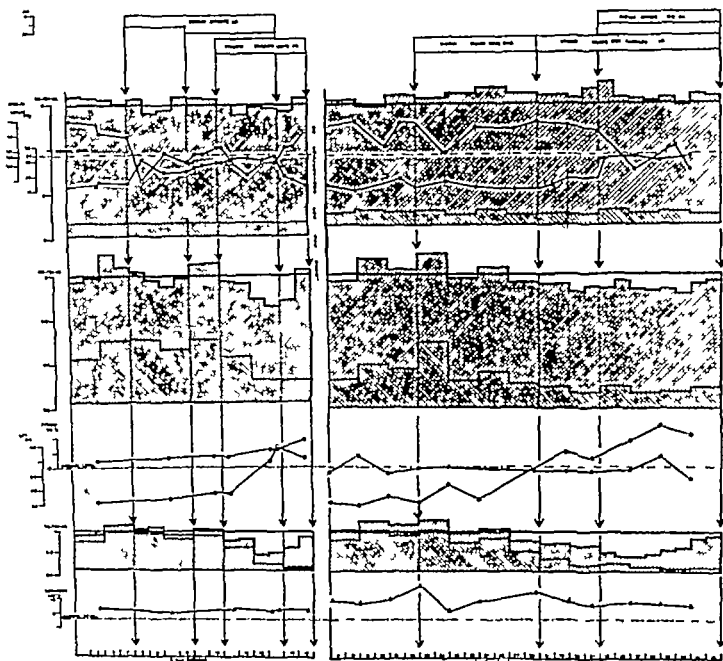


FIG 33 EXPERIMENT 3 CASE 5, RENAL ACIDOSIS, RICKETS

Effect of alkaline therapy with and without vitamin D and of vitamin D therapy with and without alkaline therapy on calcium and phosphorus metabolism. For discussion see text.

fact that the urinary calcium excretion was essentially normal during the control periods (1 through 4 and 17 through 22). Most individuals left to their own devices, of course, would select an acid ash diet. It is not surprising, therefore, that this patient was in calcium balance during the first four control periods, and that her urinary calcium excretion in period 4 was only 63 mg/day. With the administration of 200 m.eq. of sodium citrate during periods 5 to 8 there was a slight trend to a more positive calcium balance and the urinary calcium excretion

during period 8 averaged 43 mg /day as compared with the 63 mg during period 4. During periods 9 and 10 an additional 100 m eq of sodium citrate were given but there was no further decrease in the calcium excretion, in fact, a slight rise. But with the administration of vitamin D in periods 11 through 14 there was a

TABLE 3  
*Metabolic data for experiment 3*

PERIOD	CALCIUM PER 24 HR					PHOSPHORUS PER 24 HR					NITROGEN PER 24 HR					TREATMENT	
	Urine	Feces	T exct	Int	Bal	Urine	Feces	T exct	Int	Bal	Urine	Feces	T exct	Int	Bal	Acid base salts	Vitamin D
	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	gm	gm	gm	gm	gm	m eq /24 hr	units
1	54	259	314	355	+41	346	197	543	573	+30	8 492	0 878	9 37	8 78	-0 59	NaCl 200	
2	61	259	320	355	+35	305	197	562	573	+11	8 341	0 878	9 22	8 78	-0 44	NaCl 200	
3	58	345	403	355	-48	303	279	672	573	-99	8 227	0 878	9 11	8 78	-0 33	NaCl 200	
4	63	345	408	355	-53	332	279	611	573	-38	7 953	0 878	8 83	8 78	-0 05	NaCl 200	
5	37	339	376	355	-21	302	284	586	573	-13	8 284	0 878	9 16	8 78	-0 39	Na citrate 200	
6	54	339	393	355	-38	269	284	553	573	+20	7 359	0 878	8 24	8 78	+0 54	Na citrate 200	
7	47	283	330	355	+25	286	237	523	573	+50	7 564	0 878	8 44	8 78	+0 34	Na citrate 200	
8	43	283	326	355	+29	323	237	560	573	+13	8 490	0 878	9 37	8 78	-0 59	Na citrate 200	
9	55	315	370	355	-15	338	284	622	573	-49	8 398	0 878	9 27	8 78	-0 49	Na citrate 300	
10	51	315	366	355	-11	348	284	632	573	-59	8 279	0 878	9 16	8 78	-0 38	Na citrate 300	
11	63	211	274	355	+81	341	205	546	573	+27	7 918	0 878	8 80	8 78	-0 02	Na citrate 300	300,000
12	75	211	286	355	+69	329	205	534	573	+39	7 235	0 878	8 11	8 78	+0 67	Na citrate 300	300,000
13	85	58	143	355	+212	363	101	464	573	+109	7 757	0 878	8 64	8 78	+0 14	Na citrate 300	300,000
14	105	58	163	355	+192	324	101	425	573	+148	7 029	0 878	8 51	8 78	+0 27	Na citrate 300	300,000
15	186	27	213	355	+142	359	99	458	573	+115	7 505	0 878	8 38	8 78	+0 40	NaCl 200	300,000
16	282	27	309	355	+46	501	99	600	573	-27	8 333	0 878	9 21	8 78	-0 43	NaCl 200	300,000
Interval of 655 days																	
17	93	275	368	355	-13	345	198	543	595	+52	7 508	0 863	8 37	8 10	-0 27	NaCl 200	
18	84	369	453	355	-98	398	299	697	595	-102	6 954	1 064	8 02	8 10	+0 08	NaCl 200	
19	90	327	417	355	-62	365	263	628	595	-33	7 799	0 898	8 70	8 10	-0 60	NaCl 200	
20	91	370	461	355	-106	383	347	730	595	-135	7 542	0 984	8 53	8 10	-0 43	NaCl 200	100,000
21	93	253	346	355	+9	375	189	564	595	+31	8 142	0 671	8 81	8 10	-0 71	NaCl 200	100,000
22	85	289	374	355	-19	390	245	635	595	-40	8 214	1 001	9 22	8 10	-1 12	NaCl 200	100,000
23	103	168	271	355	+84	370	162	532	595	+63	8 092	0 706	8 80	8 10	-0 70	NaCl 200	100,000
24	132	109	241	355	+114	383	143	526	595	+69	7 833	0 764	8 65	8 10	-0 55	NaCl 200	300,000
25a	171	47	218	355	+137	377	102	479	595	+116	7 839	0 669	8 51	8 10	-0 41	NaCl 200	300,000
25b	170	47	217	355	+138	402	102	504	595	+91	8 379	0 669	9 05	8 10	-0 95	NaCl 200	300,000
26a	101	59	160	355	+195	356	145	501	595	+94	8 525	0 972	9 50	8 10	-1 40	Na citrate 200	300,000
26b	76	59	135	355	+220	397	145	542	595	+53	7 548	0 972	8 52	8 10	-0 42	Na citrate 200	300,000
27a	97	33	130	355	+225	388	102	490	595	+105	7 621	0 771	8 39	8 10	-0 29	Na citrate 200	300,000
27b	122	33	155	355	+200	383	102	485	595	+110	7 527	0 771	8 30	8 10	-0 20	Na citrate 200	300,000
28a	171	20	191	355	+164	381	108	489	595	+106	7 635	0 879	8 51	8 10	-0 41	Na citrate 200	300,000
28b	186	20	206	355	+149	353	108	461	595	+134	7 162	0 879	8 04	8 10	+0 06	Na citrate 200	300,000
29a	281	25	306	355	+49	473	101	574	595	+215	8 026	0 733	8 76	8 10	-0 66	Na citrate 200	300,000
29b	306	25	331	355	+24	476	101	577	595	+18	7 849	0 733	8 58	8 10	-0 48	Na citrate 200	300,000

marked fall in the fecal calcium excretion, (58 mg for period 14 as compared with 315 mg for period 10) as expected, and only a comparatively slight rise in the urinary calcium excretion (105 mg for period 14 as compared with 51 mg for period 10), consequently, the patient went into strongly positive calcium balance (192 mg in period 14). Finally in periods 15 and 16, when the sodium citrate was discontinued while the vitamin D was continued, there was a further slight

decrease in fecal calcium excretion coupled now with a marked rise in the urinary calcium excretion (282 mg in period 16 as compared with 105 mg in period 14) which almost wiped out the positive calcium balance obtained by the increased calcium absorption. These findings emphasize the importance of administering both therapeutic agents together (an alkalinizing salt and vitamin D).

During periods 17 through 42 the same experiment was repeated in reverse order, i.e. after the control period the patient received vitamin D alone first and then vitamin D plus sodium citrate. The anticipated findings, with a few reservations, were obtained. With vitamin D alone there was a marked fall in fecal calcium excretion and a marked rise in urinary calcium excretion, since the latter did not offset the former, the patient went into strongly positive calcium balance (see period 34). When sodium citrate was added to vitamin D in period 35 there was a marked fall in the urinary calcium excretion as expected and a resulting marked increase in the positive balance (220 mg in period 36 as compared with 138 mg in period 34). However, the decrease in the urinary calcium excretion persisted for only two 3-day periods (35 and 36) after the onset of sodium citrate therapy, from period 36 through period 42 there was a steady rise in the urinary calcium excretion so that the positive calcium balance was almost wiped out in period 42. The authors attribute this unexpected finding to the supposition that the bony tissue by period 37 had become entirely calcified and that there was, therefore, no place in the skeleton for calcium to go, accordingly, just as when vitamin D is administered to a normal individual, the calcium which was absorbed in increased amount from the gastro-intestinal tract was promptly reexcreted in the urine.

The urinary potassium excretions were determined for the first eight periods (see table 3). It will be noted that they tended to parallel the urinary calcium excretions, this was particularly true in period 5 when there was a marked fall in both on the initiation of sodium citrate therapy.

The serum calcium and phosphorus values are of interest. In both parts of the experiment when a strongly positive calcium balance was obtained it was the serum phosphorus which rose and not the serum calcium. This is in agreement with the thesis expounded above that the low serum phosphorus represents a compensatory over-activity of the parathyroid tissue in an effort to keep the serum calcium level normal. With an increased calcium balance this need is lessened and the serum phosphorus rises.

*Experiment 4—Total acid-base balance of urinary electrolytes during first sixteen periods of experiment 3*

In order to throw further light on the deranged electrolyte metabolism in the specific type of renal acidosis under discussion, it was decided to balance acid electrolytes in the urine against the basic electrolytes according to the principles described by Gamble (50). On the basic side were determined total base, ammonia, and titratable acidity, on the acid side organic acid, phosphate, sulphate, chloride, and  $\text{CO}_2$ . The phosphate values are adjusted to their base binding values at a pH of 7.35 (i.e. a valence of 1.8 instead of 3.0 is assumed). All values

are expressed in milliequivalents. By subtracting the sum of the acid values from the sum of the basic values the "undetermined acid" ( $u a$ ) is derived. In addition, the "titratable-acidity-minus- $CO_2$ " was determined, when the  $CO_2$  value is added to this value one obtains indirectly the titratable acidity. This derived value for titratable acidity is more accurate than the one determined when the titratable acidity is low or actually negative as is the case at alkaline pH's.

The urine was collected under oil and kept in the ice-box until the 24-hour collection was complete. The determinations of ammonia,  $CO_2$ , pH (glass electrode), organic acid, and titratable-acidity-minus- $CO_2$  were carried out at once. The diet itself remained constant throughout the sixteen 3-day periods and with the added calcium gluconate constituted an intake which was slightly alkaline in ash (2.2 m eq), the addition of sodium citrate during periods 5 through 14, of course, made the intake, as a whole, during these periods very alkaline. The data are shown in table 4 and fig. 34.

Fig. 34 is self-explanatory. The findings on the whole are as anticipated. Note especially during the four control periods, in spite of the high chloride and the low  $CO_2$  levels in the blood, that the ammonia excretion only reached 47.0 m eq per 24-hours (cf. value of over 100 m eq for normal man receiving ammonium chloride in experiment 2) and that the titratable acidity only reached 11 m eq/24 hours. A somewhat disturbing feature of these data are the high values for "undetermined acid." To be sure, these values contain the summated errors of the entire experiment. Though these values for undetermined acid do rise considerably as the urine becomes alkaline, it is unlikely that their unexplained magnitude is entirely due to errors in the collection of  $CO_2$ , since the values were already high during the control periods when the  $CO_2$  was very small. The undetermined acid presumably is not some organic acid since the latter was estimated separately (method of Van Slyke and Palmer (55)).

The most interesting features of fig. 34 are highlighted in fig. 35 and 36.

Fig. 35 contains an analysis of the chloride, sodium, and total base data. It will be seen in period 5 when 200 m eq of chloride were replaced by citrate, the sodium intake remaining unchanged, that the fall in the urinary chloride excretion did not quite equal the decrease in the chloride intake and the serum chloride fell. At the same time, it will be seen, there was a fall (32.0 m eq) in the urinary excretion of total base. Of this 32 m eq fall, 10 m eq were accounted for by the fall in the potassium excretion and 1 m eq by the fall in calcium excretion. In period 9, when the sodium intake was increased, the chloride intake remaining constant, the rise in the total base excretion did not correspond with the change in intake and the serum total base level rose, the chloride excretion showed little if any change. The administration of vitamin D had no apparent effect on the total base or chloride excretions. In period 15 when the intake was returned to the control level there was a rapid adjustment back to the control levels.

In fig. 36 an analysis is made of the determined  $CO_2$  values and those calculated from the urinary pH's according to the precepts laid down by Gamble (51) and



TABLE 4  
Metabolic data for experiment 4

Osmolality	ID.M.	INTAKE PER 24 HR.		ACTIVITY OF DIET PER 24 HR.	URINE CATIONS PER 24 HR.								URINE ANIONS PER 24 HR.						CALCULATED CO <sub>2</sub> PER 24 HR.	SERUM						TREATMENT																																																																																																																																																																																																																																																																																																																																																																																																																																																							
		Na	Cl		T.B.	Ca	K	NH <sub>4</sub>	Tl. ac. CO <sub>2</sub>	Tl. ac. CO <sub>2</sub> + CO <sub>3</sub>	Tl. ac. CO <sub>2</sub> + CO <sub>3</sub>	Org. ac.	PO <sub>4</sub>	SO <sub>4</sub>	Cl	CO <sub>2</sub>	U.A.	URINE pH		mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. Hg	mm. H

Valence 1.8.

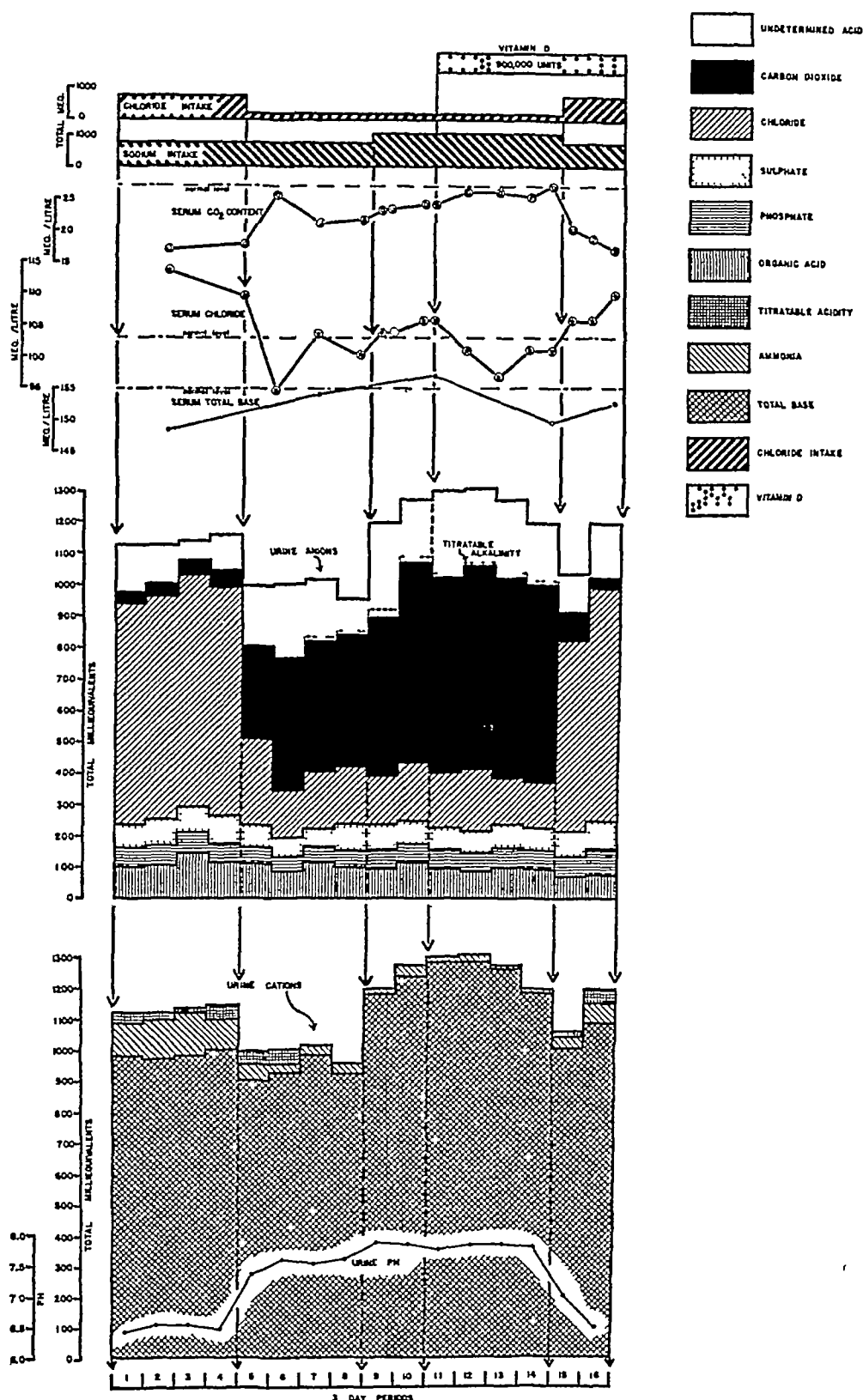


FIG 34 EXPERIMENT 4 CASE 5, RENAL ACIDOSIS, RICKETS  
 Effect of alkaline therapy, alkaline therapy plus vitamin D, and vitamin D alone on total acid base electrolyte balance in urine For discussion see text

discussed above. The authors use 4.2 volumes per cent as the concentration of  $\text{H}_2\text{CO}_3$  in the urine. This value is the average of 55 determinations performed by Gamble, his individual determinations having a range of 5.3 to 3.3 volumes per cent.

It will be noted that the determined and derived  $\text{CO}_2$ 's coincide fairly well until the urine becomes alkaline when the derived values rise considerably above

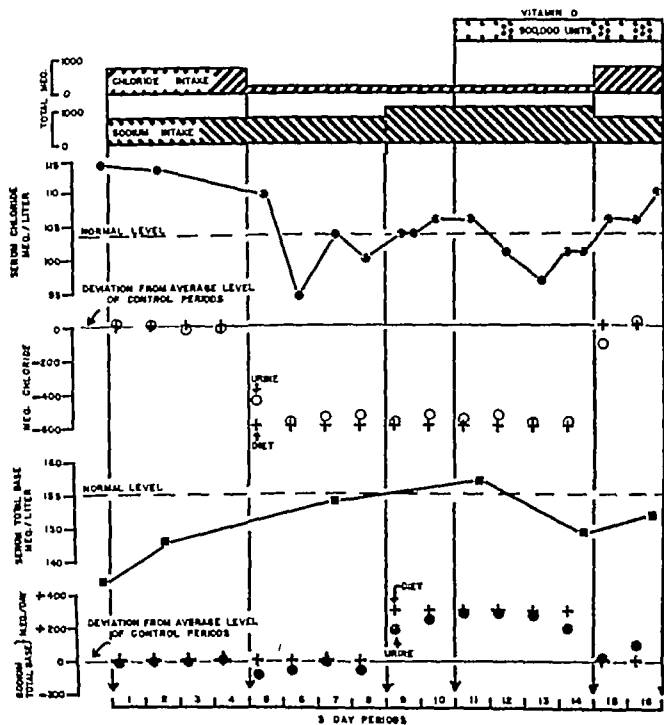


FIG 35 EXPERIMENT 4 CASE 5, RENAL ACIDOSIS WITH RICKETS

A closer analysis of chloride, sodium, total base data (compare fig 34). The data charted at the very bottom of the diagram are the deviations of the sodium intake from the average of the control periods and the deviations of the total base output from the average of the control periods. For further discussion see text.

the actual values. Thus, on the second day of period 12 the calculated  $\text{CO}_2$  is 111 meq/liter and the determined only 84.8 meq/liter. This discrepancy could be obliterated if one assumes an  $\text{H}_2\text{CO}_3$  content of the urine of 3.2 instead of 4.2 volumes per cent, the slight unavoidable loss of  $\text{CO}_2$ , which must occur would make a change in this direction. It seems unlikely that the discrepancy is to be attributed to a loss of  $\text{CO}_2$  after the determination of the urinary pH and before

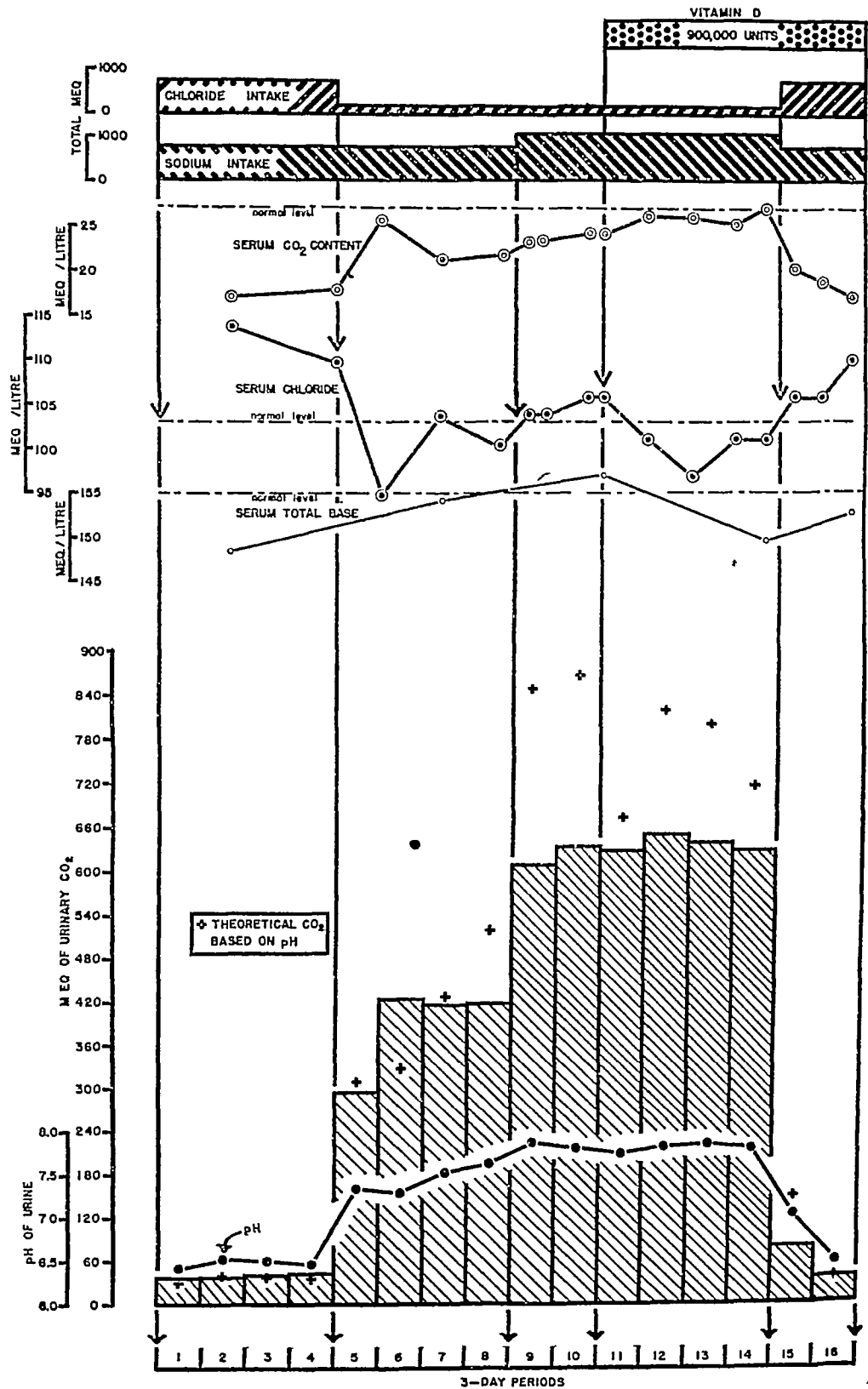


FIG 36 EXPERIMENT 4 CASE 5, RENAL ACIDOSIS WITH RICKETS  
A comparison of CO<sub>2</sub> found in urine with CO<sub>2</sub> calculated from pH of urine For discussion see text

the determination of the  $\text{CO}_2$ . An error in the pH determination of the urine such as an actual pH of 7.74 instead of 7.87 would likewise account for the discrepancy. One cannot explain the discrepancy at the higher pH's on the basis that the  $\text{CO}_2$  tension in the blood and hence in the urine is higher because this would make a shift in the opposite direction. The authors, however, wish to stress the relatively good agreement, all things considered, which they found between the calculated and determined values for  $\text{CO}_2$  in the urine, they feel that these data lend support to Gamble's postulation that carbonic acid in urine is approximately stationary and that, therefore, the quantity of bicarbonate is a direct function of pH.

It is of interest that the  $\text{CO}_2$  in the urine rose from 13 to 139 m eq/day when the amount of chloride in the intake was reduced by 200 m eq/day and rose further to 216 m eq/day when there was an additional increase of 103 m eq/day in the sodium intake, thus the net gain of base not bound by  $\text{CO}_2$  was 74 m eq/day after the first change and 102 m eq/day after the second change. Since the serum  $\text{CO}_2$  did not return to normal until after the second change, it seems clear that the kidneys in this case excrete an alkaline urine and waste base in combination with  $\text{CO}_2$  at a time when there is still a blood acidosis present. The authors conclude that the kidneys in this patient have a decreased ability to excrete an acid urine, as well as to make ammonia, if one takes into account the degree of blood acidosis at the time the determinations are made.

The following four case histories illustrate further some of the points discussed concerning this syndrome.

*Case 6* Diagnoses renal acidosis, nephrocalcinosis, pyelonephritis (*Staph. albus* and *B. coli*), chemical-osteomalacia without-high-phosphatase.

Miss A. St. P., M.G.H. #311058, a single woman of 28, entered the hospital on July 15, 1941 complaining of bilateral pain in the region of the kidneys, dysuria, hematuria, and the passage of gravel of about 4 months duration. Frequency and nocturia had started about 4 years previously and she had first developed bilateral flank pains 1 year previously following a cold.

In her past history, she had always been rather sickly and had had the usual childhood diseases including scarlet fever. Of especial interest as it suggests a low serum potassium is the history of paralysis of the arms and legs of 3 days duration about 8 years previously which disappeared spontaneously.

Physical examination was non-contributory except for very short stature, blood pressure was 130/80.

Laboratory studies: urine,—slight albuminuria, slight pyuria, hyposthenuria (specific gravity 1.010 during a concentration test), phenolsulphonphthalein excretion 10 per cent in 15 minutes and 40 per cent in one hour, urine culture,—*Staphylococcus albus* and *B. coli*, serum chemistry,—calcium 9.7 mg/100 cc, phosphorus 2.3 mg/100 cc, alkaline phosphatase 4.8 Bodansky units,  $\text{CO}_2$  combining power 18 m eq/liter, chloride 117.0 m eq/liter, protein 6.8 gm/100 cc, non protein nitrogen 16 mg/100 cc, sodium 139.0 m eq/liter, analysis of a stone,—phosphorus + + + +, uric acid 0, oxalate trace, red count 4,900,000 white count 8,000.

X-rays showed bilateral nephrocalcinosis (see Fig. 21C). There were no skeletal changes.

It was felt that the findings could all be explained on the basis of renal acidosis. With a low serum phosphorus and a normal serum phosphatase a diagnosis of chemical-osteomalacia without-high-phosphatase was made. Accordingly she was given one teaspoonful of sodium citrate crystals four times daily, her  $\text{CO}_2$  combining power rose to 26 m eq/liter.

and her serum chloride fell to 106 m eq /liter Her serum phosphorus returned to normal She was changed from a sickly individual to an energetic young person She continued to pass calculi but formed no new ones so that when last seen October 13, 1944 the number of calculi was markedly reduced (see fig 22)

*Case 7* Diagnosis renal acidosis, nephrocalcinosis, osteomalacia, decreased stature

Miss B A , M G H #398314, age 18, entered the Baker Memorial Hospital on March 29, 1943, having been referred by Dr Richard S Hawkes of Portland, Maine She complained of skeletal pain and the passage of kidney stones

The patient dated the onset of her present illness to 9 years previously when she first developed an intermittent pain in her right side diagnosed as appendicitis and treated without relief by an appendicectomy, thereafter she practically stopped growing and continued to have frequency, nocturia, and some dysuria She consulted a chiropractor who treated her for a hip condition with manipulations but without improvement

Two years before admission she fractured several ribs while turning over in bed, later she fractured her left leg Nine months before admission she was admitted to the Maine General Hospital where a bilateral osteotomy of the femurs was performed in order to straighten her legs which had been bowed for an indefinite period of time, the fractures failed to heal, however, (see fig 26) and she became bed-ridden

Five months before admission she started passing calculi of which she brought a bottle full with her

The points of interest in her past history were scarlet fever at the age of 5, enuresis since childhood, nocturia and dysuria as long as she could remember, and menarche at the age of 12

On physical examination she was a frail young woman, 4 ft 3 in in height, with marked rachitic deformities of the skeleton, normal sexual development, and blood pressure of 120/90, physical examination was otherwise non-contributory

Laboratory studies urine,—slight albuminuria, no glycosuria (glucose tolerance test normal at a later date), specific gravity up to 1 008 in a concentration test, slight pyuria, urine culture,—no growth, phenolsulphonphthalein excretion relatively good,—15 minutes 15 per cent, 30 minutes 15 per cent, 1 hour 20 per cent making a total of 50 per cent, urine negative for cystine, haemoglobin 16 4 gm , white count 6,300, blood smear not remarkable, serum chemistry,—non-protein-nitrogen 16 mg /100 cc , calcium 10 4 mg /100 cc , phosphorus 1 9 mg /100 cc , alkaline phosphatase 21 Bodansky units, protein 7 1 gm /100 cc , sodium 138 m eq /liter, chloride 115 6 m eq /liter, CO<sub>2</sub> 13 8 m eq /liter, prothrombin time normal, analysis of the stones,—strongly positive test for phosphorus and negative tests for uric acid and oxalate

X-rays showed generalized demineralization, poor calcification of both osteotomy calluses at lower ends of the femurs (see fig 26B), bilateral nephrocalcinosis (see fig 21D), stones at the lower end of the right ureter (see fig 27A), scoliosis of the spine, narrowing of the pelvis, coxa vara deformities of the upper ends of the femora, united but uncalcified fractures in the pubic bone (see fig 27A), multiple similar fractures of the ribs, symmetrical fractures of the surgical necks of both humeri, and moderately well-preserved lamina dura

The patient received large amounts of alkali (sodium citrate, 1 teaspoonful 4 times daily), large amounts of vitamin D (circa 3 mg of vitamin D<sub>2</sub> daily), and a goodly amount of calcium in the form of milk Her skeleton responded very well (see fig 27) and she walked out of the hospital on July 28, 1943 approximately 4 months after entering On March 3, 1945 the serum calcium was 9 0 mg /100 cc , the serum phosphorus 2 9 mg /100 cc , and the serum alkaline phosphatase 3 5 Bodansky units

*Case 8* Diagnoses renal acidosis, hypokaliëmic syndrome, chemical osteomalacia

The first two admissions, in October and November of 1943 respectively, of J J F , M. G H #424023, a married man of 40, were to the Neurological Service for symptoms which were finally diagnosed by Dr. K P Bird on the second admission as being due to hypo-

kaliemia (see Brown et al (41)) On October 13 1943 two days before his first admission the patient noted weakness of his left leg with pain in the muscles there was also some back pain, on the following day his arms and legs became paralyzed—the left more than the right. The symptoms were improved by prostigmine. Neurological examination was non-contributory except for a Horner's syndrome on the right. A lumbar puncture revealed no abnormalities in the spinal fluid. The symptoms rapidly cleared up after admission to the hospital and he was discharged without a definite diagnosis having been arrived at on October 26, 1943. He entered the hospital again with essentially the same symptoms and findings on November 11, 1943.

In his past history, he had had a penile lesion, a urethral discharge and an epididymitis at 20, a traumatic hematuria at 25, ureteral colic with passage of gravel at 35 and a recently acquired alcoholism with morning vomiting and loss of weight.

Physical examination was non-contributory except for the findings associated with hypokaliemia. His blood pressure was 112/80.

Laboratory studies: urine—moderate albuminuria, slight pyuria, no glycosuria, marked hypercalcaemia as shown by Sulkowitch tests, fixation of pH at 6.5 to 7.0, specific gravity of 1.018 during a urine concentration test, phenolsulphonphthalein excretion excellent of 1.018 during a urine concentration test, 80 per cent in 2 hours, serum levels (some of the following at a later date)—potassium 2.5 m eq/liter (normal circa 5 m eq/liter), calcium 8.8 mg/100 cc, phosphorus 2.7 mg/100 cc, phosphatase 5.5 Bodansky units, sodium 141.0 m eq/liter, chloride 110.0 m eq/liter,  $\text{CO}_2$  content 18.8 m eq/liter, total protein 6.0 gm/100 cc, non protein nitrogen 24 mg/100 cc, red count 5.1 million, white count 9,700, analyses of the calculi—a strongly positive test for phosphate and a very weak test for oxalate, repeated specimens for urine culture—no organisms in the smear, Staphylococcus on culture of most of the specimens, Hinton test for syphilis negative, electrocardiograms—low T wave characteristic of hypokaliemia and a reversion to a normal tracing after the latter condition was corrected.

X rays showed normal density of the skeleton, bilateral renal calculi and rather poor dye excretion by the kidney.

The diagnosis of renal acidosis resulting from tubular insufficiency without glomerular insufficiency with a complicating hypokaliemia and possibly a pyelonephritis was made. In addition he had chemical-osteomalacia with high phosphatase. Accordingly he was started on one teaspoonful each of sodium citrate, potassium citrate and calcium gluconate daily. On this regime the pH of his urine rose to 7.5, the serum  $\text{CO}_2$  content rose to normal and the serum chloride fell to normal, the serum phosphorus rose and the serum phosphatase fell, calcium disappeared from his urine, the albuminuria also disappeared.

Later because of the possibility of an underlying low grade pyelonephritis he was given a course of penicillin therapy. The urine culture became negative during this therapy but later reverted and it is questionable whether this therapy had any permanent effect. Following this course of therapy he was taken off alkali, this was followed by another attack of hypokaliemia, a recurrence of hypercalcaemia and albuminuria and the passage of more stones. The patient went back on alkali and these findings again cleared up.

**Case 9** Diagnoses: renal acidosis, osteomalacia, hypokaliemia, nephrolithiasis.

The patient M. B. M.G.H. #202252, a single girl of 23, entered the Massachusetts General Hospital on the Arthritic Service in August 1939 complaining of back trouble. She traced the onset of her illness to a ride in a roller-coaster two years previously, following which she developed pain in her back. The pain spread to her hips and she developed a limp. She was not improved by therapy prescribed by a chiropractor, crutches were tried for 8 weeks without benefit. Later she became very weak and lost weight.

Her past history was irrelevant except for passage of gravel in her urine at the age of 10.

The authors are indebted to Dr. William Beckman for bringing this case to their attention and for permission to use it.

On physical examination the pertinent findings were undernutrition, a stiff back which led to the diagnosis of spondylitis, and a blood pressure of 120/70

Laboratory studies urine,—albumen ++, specific gravity 1 004 to 1 012, pyuria, urine culture,—no growth, serum chemistry,—non-protein-nitrogen 28 mg /100 cc, calcium 9 7 and 10 1 mg /100 cc, phosphorus 2 8 and 2 2 mg /100 cc, alkaline phosphatase 8 4 and 9 2 Bodansky units, sodium 145 0 and 142 0 m eq /liter, chloride 117 0 m eq /liter,  $\text{CO}_2$  combining power 20 0 m eq /liter, protein 8 6 gm /100 cc, red count 4 5 million, haemoglobin 80 per cent of normal, white count 7,200

By x-ray the spine was remarkable only in that the dorsal spine was straight and that there was a slight scoliosis in the lumbar region, the right twelfth rib showed a transverse fracture line with callus formation (see fig 37), a similar fracture was present in the right scapula (see fig 37B) but was not noticed at the time, there were stones in the left kidney, an intravenous pyelogram confirmed the stones in the left kidney and showed a good functioning right kidney and a rather poorly functioning left kidney, a retrograde pyelogram failed to show hydronephrosis on the left

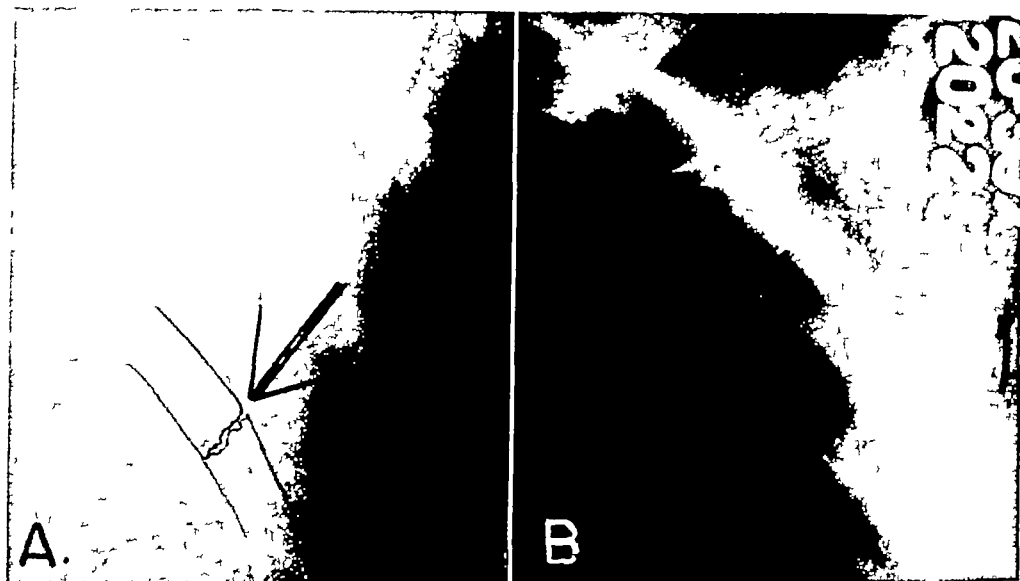


FIG 37 CASE 9 RENAL ACIDOSIS, MILKMAN'S SYNDROME

Note fracture lines in right scapula and right twelfth rib (arrows) Note good density of bones in spite of florid osteomalacia

With the albuminuria, pyuria, high serum chloride, low serum  $\text{CO}_2$ , low serum phosphorus, and high serum phosphatase, it is now easy in retrospect to make the diagnosis of osteomalacia secondary to renal acidosis

This diagnosis, however, was not made and the patient was given three liters of 5 per cent dextrose in normal saline on September 4, a liter and one-half of normal saline on September 5, and the same amount again on September 6. As demonstrated by Albright, Consolazio, Coombs, Sulkowitch, and Talbott (43) the taking of NaCl increases an acidosis such as this one secondary to tubular insufficiency and, to be sure, this patient's condition did grow rapidly worse. On September 6 the record states that "motion and strength in extremities is normal at times but patient complains of great weakness—even paralysis—much of the time", it goes on to state that patient "calls nurses incessantly to move her head, her arms, or her legs". These bizarre symptoms were almost certainly due to a low serum potassium, unfortunately no potassium determination was made. The following day the patient became stuporous and was seen by Dr William Beckman who advised parenteral alkali therapy, but she died before this was given. The chemistry of her serum taken shortly before death showed chloride 128 m eq /liter,  $\text{CO}_2$  combining power 13 0 m eq /liter, sodium 151 m eq /liter, protein 8 gm /100 cc, calcium 9 mg /100 cc, phosphorus 1 5 mg /100 cc, and alkaline phosphatase 8 2 Bodansky units



It is clear, therefore, that the acidosis had markedly increased, presumably due to the saline intravenously. It is not unlikely that the patient had terminally a very low serum potassium level and that this accounted for the symptoms suggesting paralysis, unfortunately no potassium determination was done.

Autopsy showed nephrolithiasis, chronic pyelonephritis, parathyroid hyperplasia, florid osteomalacia (see fig 38), and acute necrosis with question of infarction of the pons.

Since the kidney pathology is thought to be the primary factor in the syndrome under discussion, the kidney findings are reported in more detail.<sup>12</sup> The right kidney weighed 275 gm and the left 150 gm, the capsules stripped with some difficulty, the cortices measured 5 mm in thickness, the pelvis were negative, there were two stones lying free in the calices of the left kidney. On microscopic examination the majority of the glomeruli seemed normal, where pathology was present it varied from capsular thickening to complete fibrosis of the capillary tuft. The tubules were damaged most severely in their

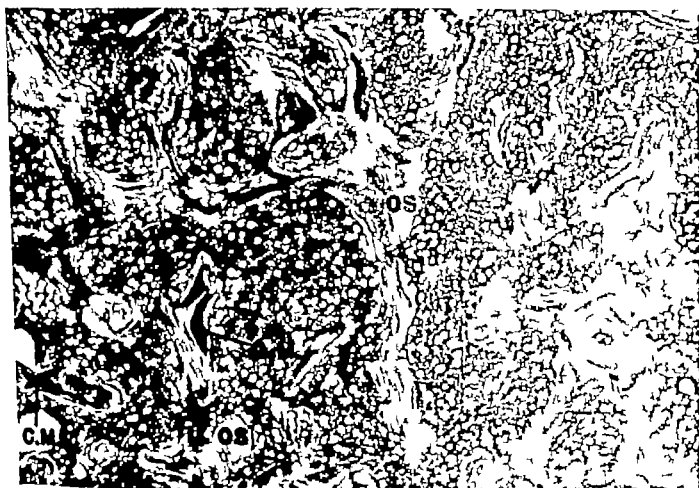


FIG 38 CASE 9, RENAL ACIDOSIS OSTEOMALACIA  
Photomicrograph of vertebral changes at autopsy. Note that the trabeculae are surrounded with osteoid (os) which prevents any calcified matrix (cm) from reaching the surface.

proximal and distal convoluted portions. The cells of the convoluted tubules were swollen, finely granular, and contained vacuoles and an occasional hyaline droplet in the cytoplasm. There were a few large groups of dilated tubules lined with atrophic epithelium and filled with so-called colloid casts—findings characteristic of chronic renal tubular degeneration. The interstitial tissues showed patchy infiltration with polymorphous cells, atrophied and eosinophiles, lymphocytes, and plasma cells. The blood vessels were not remarkable except for an occasional thickened arteriole. The most impressive feature was the vacuolization in the convoluted tubules, especially the distal portions which because of its extreme degree and the accompanying granularity, was thought not to be a post mortem change. The latter could not definitely be ruled out.

<sup>12</sup> The authors are indebted to Dr. Marshall D. Ruffin for the gross autopsy, to Dr. Ronald C. Sniffen and Dr. Benjamin Castleman for the microscopic findings.

RENAL ACIDOSIS OF THE FANCONI SYNEROME TYPE

The authors have had no personal experience with late rickets or osteomalacia resulting from the Fanconi syndrome, their remarks are based largely on the excellent review by McCune, Mason, and Clarke (56). These authors credit Fanconi as being the first to invoke a renal tubular insufficiency to account for the pathogenesis of several examples of intractable normoazotemic, hypophosphatemic rickets accompanied by chronic acidosis and renal glycosuria.

It would appear that the tubular acidosis associated with the Fanconi syndrome is entirely different from the tubular acidosis discussed in the preceding section. Thus, in the Fanconi syndrome the acidosis is due to an excess of organic acids being presented to the kidneys for excretion, in the other syndrome the acidosis is due to a decreased ability of the kidneys to make ammonia and to excrete an acid urine. Therefore, one would expect increased organic acids, increased ammonia and increased titratable acidity in the urine in the Fanconi

TABLE 5  
*Findings in patient 5 with renal acidosis resulting from tubular-insufficiency-without-glomerular-insufficiency contrasted with findings of patient with Fanconi syndrome reported by McCune et al (57)*

CONDITION	SERUM (M.EQ / LITER)		URINE			
	Cl	CO <sub>2</sub>	pH	$\frac{\text{Amm N}}{\text{Tot N}} \times 100$	Tit Ac m eq / kg / 24 hrs	Organic acid m eq / kg / 24 hrs
Normal	104	27	4.5-7.8	4		1
Renal acidosis, case 5	113	17	6.4-6.5	7	0.12-0.29	1
Fanconi syndrome case of McCune et al (57)	104	19	4.8-6.8	24	1.25-2.50	10

syndrome, normal amounts of organic acid, decreased ammonia and decreased titratable acidity in the urine in the syndrome discussed in the preceding section, and an increased calcium in the urine in both syndromes. In table 5 a comparison is made between the findings in case 5 and those in the case reported by McCune et al (56). It will be seen that the findings were as expected.

McCune et al (56) found that 82 per cent of the organic acid in the urine was amino acid, 11 per cent lactic acid, and 7 per cent beta-hydroxybutyric acid. They point out that the beta-hydroxybutyric acid could be explained by the hypoglycemia resulting from renal glycosuria. Furthermore, several cases of the Fanconi syndrome have shown at autopsy cystine deposits in the reticulo-endothelial system which again suggests a disorder in the amino acid metabolism. Whether or not these cases show cystinuria seems not to have been definitely established. McCune et al interpret the data to indicate diminished ability of the tubular epithelium to reabsorb dextrose, amino acids, and phosphates, but point out that the hyperphosphaturia may be the result of a secondary hyperparathyroidism. In fig. 39 is depicted a possible interpretation of the inter-relationship

ships in the disordered homeostasis in the Fanconi syndrome, fig 39 is to be compared with fig 23, a similar diagram for the other type of renal acidosis leading to late rickets or osteomalacia. In fig 39 the hyperphosphaturia is ascribed to a secondary hyperparathyroidism although the explanation of McCune et al has much to recommend it

As regards treatment, McCune et al came to no definite conclusion. The authors would anticipate that the osseous disorders would respond to the same measures as used for the other type of renal acidosis,—namely, alkali, plus high calcium intake, plus vitamin D

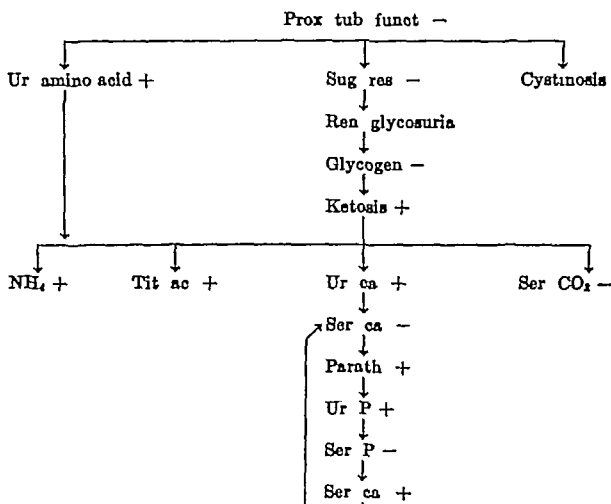


FIG 39 DIAGRAM OF DISORDERED HOMEOSTASIS IN FANCONI SYNDROME  
Compare with fig 23

#### OSTEOMALACIA RESULTING FROM HYPER-CALCURIA WITHOUT HYPER-CALCEMIA AND WITHOUT RENAL ACIDOSIS

There seems to be a not inconsiderable number of cases wherein the primary defect in metabolism is a propensity on the part of the kidneys to excrete an increased amount of calcium for any given level of calcium in the serum. Such, to be sure, is the finding in those cases secondary to renal acidosis (*vide supra*). However, the cases under discussion do not have an acidosis and the calcium excretion in the urine, in contrast to the finding in cases with acidosis, is not decreased by alkali therapy (see fig 17). This interesting group of cases will not be discussed in detail here, it is hoped to make it the subject for a separate paper. The sequence of events in the disordered homeostasis is the same as in vitamin D lack (see fig 14) except that the first step, instead of being decreased-calcium-

absorption, is increased-calcium-excretion, the second step in both sequences is the same, tendency-to-low-serum-calcium-level. As one might anticipate, the increased calcium excretion in the urine favors kidney stone formation and it is in the Stone Clinic that most of these cases are found. Indeed, of the following four metabolic disorders leading to increased urinary calcium excretion,—hyperparathyroidism, osteoporosis during the stage of progression, renal acidosis, and idiopathic hypercalcuria—it is the last of these which is probably the most common and accounts for the findings of Flocks (47) that hypercalcuria is very common in patients with kidney stones. Few cases proceed to a greater degree of osteomalacia than “chemical-osteomalacia-without-high-phosphatase”. But the authors have one case with kidney stones who has “chemical-osteomalacia-with high-phosphatase” and one case, other than the one whose data is presented in fig 17, who has out-and-out osteomalacia.

TABLE 6

*Summary table of laboratory tests and differential types of osteomalacia*

CONDITION	SERUM					URINE				SERUM CAROTINOIDS	VIT A & K TESTS
	Alk ptse	Ca	P	CO <sub>2</sub>	Cl	Ca	NH <sub>4</sub>	Tit. ac	Sug acct.		
“Simple” vitamin D lack	H*	N or L	L	N	N	L	N	N	0	N	N
Resistance to vitamin D	H	N or L	L	N	N	L	N	N	0	N	N
Steatorrhea	H	N or L	L	N	N	L	N	N	0	L	L
Renal acidosis (tubular insufficiency-without-glomerular-insufficiency)	H	N or L	L	L	H	H	L	L	0	N	N
Renal acidosis (Fanconi syndrome)	H	N or L	L	L	N	H	H	H	+	N	N
Idiopathic hypercalcuria	H	N or L	L	N	N	H	N	N	0	N	N
Ost fib gen after removal of parathyroid tumor	H	L	L	N	N	L	N	N	0	N	N

\* N = Normal L = Low H = High

Many of these cases have or have had pyelonephritis, whether this is the cause or the result of the condition has not yet been established.

The bone condition responds to a high calcium, high vitamin D regime, often, however, this is contra-indicated because of the nephrolithiasis.

#### OSTEOMALACIA FOLLOWING REMOVAL OF PARATHYROID TUMOR IN OSTEITIS FIBROSA GENERALISATA

This transient and rare, but academically interesting, form of osteomalacia, it is hoped, will be the subject for a paper under the joint authorship of Dr. Walter Bauer, Dr. Granville A. Bennett, and one of us (F. A.). It will be only briefly mentioned here for completion's sake.

In osteitis fibrosa generalisata due to hyperparathyroidism one has marked bone destruction and marked bone repair going on at one and the same time. Calcium is deposited in the newly formed osteoid tissue since, in spite of a low

serum phosphorus level, the serum calcium level is sufficiently high to allow for precipitation, the source of calcium and phosphorus for the newly formed bone is largely the calcium and phosphorus being set free where bone is being resorbed. Now, when one removes the parathyroid tumor there is an immediate cessation of bone destruction while bone repair continues at an accelerated rate. There is no adequate source of calcium and phosphorus and there follows a marked fall in the serum calcium level and a slight fall in the already low serum phosphorus level, the new bone which is laid down is not calcified and osteomalacia results.

#### DIFFERENTIAL DIAGNOSIS OF ETIOLOGICAL SUB GROUPS OF OSTEOMALACIA

The points in the differential diagnosis of the seven causes for osteomalacia discussed in this paper are shown in tabular form in table 6 (q v)

#### ADDITIONAL DISCUSSION

Most of the points of interest have been discussed in the body of the paper, there remains, however, one question which has disturbed the authors and may have arisen in the minds of some of the readers. Why, in osteomalacia, where the body fluids are apparently so unsaturated with respect to calcium phosphate, are not calcium ions and phosphate ions resorbed rapidly from the bones so that saturation of the body fluids is re-established? This question is all the more pertinent since in *osteitis fibrosa generalisata* the bones continue to give up calcium to the bitter end. A possible explanation may be that in osteomalacia all the trabeculae become covered with osteoid tissue which insulates the calcified matrix from the body fluids (see fig 38). The reader may then ask why do not the trabeculae in *osteitis fibrosa generalisata* become insulated with osteoid? The authors do not have even a poor explanation for this question.

#### SUMMARY AND CONCLUSIONS

1 Osteomalacia is defined as a disorder of bony tissue characterized by the failure of calcium salts to be deposited promptly in the newly formed bone matrix.

2 Osteomalacia is due to an abnormality in the body fluids in that they contain too little calcium for the level of inorganic phosphorus or too little inorganic phosphorus for the level of calcium to allow for normal precipitation of whatever calcium phosphate salt it is which is deposited in bone matrix.

3 Osteomalacia is characterized by a normal or low serum calcium level, a low serum phosphorus level, and a high serum phosphatase level, it is to be differentiated from osteoporosis where the above three levels are normal and from the *osteitis fibrosa generalisata* of hyperparathyroidism where the calcium is high instead of normal or low.

4. Milkman's syndrome, characterized by "multiple spontaneous idiopathic symmetrical fractures" is considered a form of osteomalacia for the following four reasons (a) evidence is presented that the lesions described by Milkman are united but uncalcified fractures (vide infra), such fractures are a characteristic of osteomalacia (Umbauzonen of Looser) and of no other condition, (b) the serum

calcium, phosphorus, and phosphatase findings in classical and undoubted cases of Milkman's syndrome are those of osteomalacia, (c) Milkman's syndrome responds to anti-osteomalacic therapy, and (d) the histopathology in Milkman's syndrome is that of osteomalacia (*vide infra*)

5 The biopsy from a pseudofracture of a rib from a classical case of Milkman's syndrome was shown to be osteomalacia by histological studies, bone tissue from the vertebrae of another patient at autopsy showed florid osteomalacia

6 The designation, Milkman's syndrome, is retained to emphasize the fact that a generalized disease such as osteomalacia can be present when the x-rays show no generalized decalcification but only these united but uncalcified fractures

7 Six new cases of Milkman's syndrome are presented, attention is called to the frequency with which such cases show united but uncalcified fractures of the scapulae just below the glenoid cavities

8 Cases of osteomalacia are divided into four groups according to the degree of severity, viz (1) chemical osteomalacia with low phosphatase, (2) chemical osteomalacia with high phosphatase, (3) Milkman's syndrome, and (4) advanced osteomalacia

9 Evidence (mostly from the literature) for the following seven facts concerning the action of vitamin D is presented 1) vitamin D causes a lowering in fecal calcium and phosphorus excretion, 2) the decrease in the fecal phosphorus excretion is secondary to the decrease in the fecal calcium excretion and not vice versa, 3) the decreased fecal calcium excretion is the result of an increased calcium absorption and not of a decreased calcium reexcretion into the gut, 4) the increased calcium absorption explains the rising serum calcium and increased calcium in the urine only in cases of osteomalacia and not in normal individuals or patients with hypoparathyroidism, 5) the rising serum phosphorus level following administration of vitamin D in osteomalacia is not due to the increased phosphorus absorption but to decreased parathyroid activity resulting from increased calcium absorption, 6) one cannot explain all the sequelae with vitamin D administration on increased calcium absorption but one must hypothesize a second independent action of vitamin D, namely to cause an increased phosphate excretion in the urine, it is this property of vitamin D which leads to decalcification with large amounts of the vitamin, 7) furthermore, it is this second action of vitamin D which causes the elevation of the serum calcium in the normal individual and the patient with hypoparathyroidism, in patients with their parathyroids intact this second action of vitamin D may be neutralized by the decreased parathyroid activity resulting from the increased calcium absorption of the first action of vitamin D

10 Dihydratachysterol has both of the actions of vitamin D but the ratio of the phosphorus-excretion-effect to the calcium-absorption-effect is greater with dihydratachysterol than with vitamin D, hence dihydratachysterol is the therapeutic agent of choice in the treatment of hypoparathyroidism and vitamin D is the agent of choice in the treatment of osteomalacia

11 Four causes for osteomalacia are discussed, viz (a) vitamin D lack which is subdivided into 1) "simple" vitamin D lack, 2) resistance to vitamin D, and 3)

decreased vitamin D absorption resulting from steatorrhea, (b) renal acidosis which is subdivided into 1) tubular insufficiency-without-glomerular-insufficiency, and 2) the Fanconi syndrome, (c) idiopathic hypercalcuria, and (d) a transient form of osteomalacia which follows removal of parathyroid tumor in cases of osteitis fibrosa generalisata

12 By "simple" vitamin D lack is meant a condition like the osteomalacia in China or the ordinary form of rickets in this country where the condition responds to small doses of vitamin D, no example of this condition has, to the authors' knowledge, been uncovered in the United States

13 By rickets or osteomalacia resistant to vitamin D is meant a condition where the metabolic findings are similar to those in the usual form of infantile rickets but where massive doses of vitamin D rather than small doses are required, follow up data on such a case are presented where the individual was followed through cessation of growth into adulthood. The underlying condition remained unchanged, albeit somewhat modified as to severity

14 In the osteomalacia resulting from hypovitaminosis D secondary to steatorrhea (non tropical sprue, pancreatitis, et cetera) it is emphasized that one should look for and treat deficiencies of the other fat soluble vitamins, notably vitamins K, A, and E. Two cases of Milkman's syndrome secondary to steatorrhea are presented. In one case an interesting coincidental finding—impregnation of dura with thoratrast—is demonstrated

15 The sequence of events in renal acidosis resulting from tubular-insufficiency-without-glomerular insufficiency is thought to be (a) insufficiency of renal tubules, cause unknown, (b) decreased ability to make ammonia and to excrete an acid urine, (c) demand for calcium as a base, (d) hypercalcuria, (e) tendency to hypocalcemia, (f) parathyroid hyperplasia, (g) hypophosphatemia, (h) failure to deposit calcium phosphate salts in the osteoid, and (i) osteomalacia, the condition also leads to hyperkalemia for the same reason as the hypercalcuria and secondarily to the hypokalemic syndrome, finally a high serum chloride and a low serum  $\text{CO}_2$  content are characteristic of this condition

16 The hypercalcuria resulting from tubular insufficiency without-glomerular-insufficiency may lead to nephrocalcinosis or nephrolithiasis, treatment with alkalinizing salts stops further stone formation because of decreased calcium in the urine and in spite of the alkalinization of the urine

17 Osteomalacia resulting from tubular insufficiency-without-glomerular-insufficiency responds remarkably to combined treatment with vitamin D and an alkalinizing salt, once cured, only the alkalinizing salt is necessary to prevent further bone disease, the hypokalemia responds to the alkalinizing salt alone

18 Six new cases with renal acidosis resulting from tubular insufficiency-without-glomerular insufficiency are reported. This condition is to be differentiated from so-called renal rickets (renal osteitis fibrosa) in that in this latter condition (a) the bone disease is osteitis fibrosa and not rickets, (b) there is advanced glomerular as well as tubular insufficiency, and (c) in spite of an accompanying hyperplasia of the parathyroids the serum phosphorus is high instead of low

19 A hypothesis to explain the retardation of growth in rickets is advanced, it is pointed out that this characteristic of rickets is common to cases where the etiology of the rickets is entirely different which in itself suggests that the cause of the retardation is to be found in the abnormal calcium or phosphorus metabolism

20 A discussion is included of the factors which spare base when an excess of acid is presented to the kidney for excretion and the factors which spare acid when an excess of base is presented to the kidney for excretion, the chief factors which spare base are ammonia production by the kidneys, excretion of an acid urine, and mobilization of calcium from the skeleton, the chief factor which spares acid is the excretion of bicarbonate by the kidney Since an acid sparer is a negative base sparer one gets the following equation for the sum of the base sparers (S B S )

$$\text{S B S} = \text{ammonia, plus titratable acidity, plus 49\% of the negative calcium balance, minus carbonate}$$

A method is explained whereby one can measure "titratable-acidity-minus- $\text{CO}_2$ " instead of measuring titratable acidity and  $\text{CO}_2$  separately

21 Data from the literature obtained on a "normal" individual and confirmed by new data were presented showing that (a) the S B S parallels the acidity value of the ash of the intake, (b) the S B S is an appreciably positive value on a neutral ash intake presumably because of the excretion of organic acid, (c) the calcium component of the S B S is quantitatively insignificant, (d) the titratable acidity reaches a limit depending on the amount of phosphate and organic acid in the urine and the limit to which the pH in the urine can be depressed, and (e) sodium acid phosphate by mouth fails to increase the calcium or ammonia excretion in the urine provided the individual can excrete an acid urine

22 Metabolic data are presented in which a normal individual and a patient with tubular-insufficiency-without-glomerular-insufficiency were put on the same regime and then given the same amount of acidifying salt The S B S of both individuals rose with the acidifying salt With the normal individual the rise almost compensated for the acid value of the salt and there was no change in serum chloride,  $\text{CO}_2$  content, or potassium, in the patient with renal acidosis the rise in S B S did not nearly compensate for the acidifying salt and there resulted a rise in serum chloride, a fall in serum  $\text{CO}_2$ , pH, and potassium, and a sharp rise in urinary potassium excretion

23 Other metabolic experiments on patients with renal acidosis resulting from tubular-insufficiency-without-glomerular-insufficiency are presented but are not easily summarized One conclusion drawn supports the thesis of Dr James L Gamble that the  $\text{CO}_2$  in the urine is a function of the  $\text{H}_2\text{CO}_3$  in the serum and the pH and volume of the urine

24 A short discussion of the Fanconi syndrome is included The condition is contrasted with renal acidosis resulting from tubular-insufficiency-without-glomerular-insufficiency The acidosis in the former instance is due to an excess of organic acids and in the latter to a decreased ability to excrete acid Hence,



in the Fanconi syndrome the titratable acidity and the ammonia excretion in the urine are increased rather than decreased

25 A group of cases of osteomalacia is briefly discussed in which the initial disorder is apparently a hypercalcuria without an associated hypercalcemia. The sequence of events in the disordered homeostasis is thought to be the same as with vitamin D lack except that the first step in the one case is hypercalcuria whereas the first step in the other is decreased calcium absorption. The second step in both cases is a tendency to decreased serum calcium

26 It is pointed out that the failure of the bones to keep the body fluids "saturated" with calcium phosphate in osteomalacia may be ascribed to an insulation of the calcified bone matrix from the body fluids by osteoid

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